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THRESHOLDS IN THE RELATIONSHIP OF QUADRICEPS STRENGTH WITH FUNCTIONAL LIMITATIONS IN WOMEN WITH KNEE OSTEOARTHRITIS THE MULTICENTER OSTEOARTHRITIS STUDY

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Abstract

Objective: To investigate thresholds of strength below which people with knee osteoarthritis (OA) may have more difficulty carrying out physical functions of daily life. Persons below such thresholds might benefit more from strengthening interventions than those with greater strength.

Methods: We studied persons with symptomatic OA at baseline in the Multicenter Osteoarthritis Study (MOST) who had knee extensor strength measured isokinetically at 60°/sec. Subjects

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underwent a 20-Meter walk test, a Sit-to-Stand Test and answered the WOMAC. Physical function results were plotted against measures of quadriceps strength (newton-meters, Nm) (and as strength/body weight) for the worse knee. Locally weighted regression scatterplot smoothers (LOESS) were examined for inflection points. Nonlinear relationships were examined in piecewise linear regression models. Differences were tested using linear and logistic regression models.

Results: 834 participants (65.8% women) were on average 62.9(\pm 7.9) years old. In women, there were thresholds of strength below which the slope of strength vs. function was steeper: walking speed ($<$ 58Nm), chair stand time ($<$ 32Nm) and WOMAC functions rising from a chair and getting on/off the toilet ($<$ 38Nm). We found no thresholds in men. LOESS analyses using strength/weight showed similar results.

Conclusions: In persons with symptomatic knee OA, thresholds in the strength function relationship may help identify individuals, especially women, at the brink of disability insofar as strength and daily tasks. In those with low strength, small increments in strength may be associated with improvement in function and greater ease with common daily life, emphasizing the importance of preventing loss of strength.

Studies of persons with knee OA and at risk of OA have shown that quadriceps weakness is strongly associated with functional limitations (1–3). For these individuals addressing quadriceps strength often becomes a major target of rehabilitation interventions, including general aerobic and local strengthening exercises, with the hope of improving physical function, reducing pain and physical disability, and avoiding further progression of OA (4, 5).

Although analyses may implicitly assume a linear association between strength and functional limitations (i.e. gains in strength lead to gains in function), daily tasks may require a specific amount of strength to be successfully accomplished (6, 7). This suggests the associations of quadriceps strength with measures of physical function may not be linear(8, 9); there may be “thresholds” of strength necessary to accomplish some tasks, such as rising from a chair. In weaker adults, with strength below the required threshold for the task, training may have immediate benefits in improved function, while in stronger adults, strength training may yield little apparent improvement in physical performance as the individual may already be stronger than the threshold (8–10). For stronger individuals, strength training may assist them in maintaining function or progressing to more strenuous activities.

Despite the many factors which may contribute to functional decline, including health-related behaviors, medical conditions, socio-economic status, and psychological well-being, muscle strength remains of key importance to performance (7, 9, 11). In a study employing performance-based tests of walking speed, chair stands, and standing balance in an elderly female sample, the relationship of strength to performance was independent of age, weight and height, and largely non-linear(9). Although the variance in performance explained by strength alone was less than 20% for each measure tested, with respect to the disabling process, the role played by reduction of strength was of particular importance in the weaker subset of the population (9).

Individuals with painful knee OA are often referred to physical therapy to work on strengthening with the goal of improving function and pain, as strengthening is feasible for all age groups and patients with or without comorbidities. Using data from the MOST study, the purpose of the current analysis was to identify thresholds of quadriceps strength below which performance of basic physical function tasks is adversely affected. The basic functional tasks chosen for this analysis involve quadriceps strength to move the body in opposition to gravity: rising from a chair, going up stairs, getting on and off the toilet, and walk time. We included performance-based tests where possible (walking, and rising from a chair) as well as self-reported measures of function, as these may represent different components of “function” in reflecting what people perceive they can do versus what they can actually do(12, 13). We hypothesized that across the range of quadriceps strength values, the relationship of strength and functional tasks would be non-linear. Further, we hypothesized that there exist strength thresholds for each functional task, such that below the threshold, the relationship of strength and function would be steeper than the relationship above the threshold. Strengthening might achieve a greater improvement in function for those below the threshold.

PATIENTS AND METHODS

Study Population

The Multicenter Osteoarthritis (MOST) study is a cohort study of 3026 men and women between 50–79 years of age at baseline, at risk of knee osteoarthritis (i.e. overweight, obese, a history of knee injury, or frequent knee pain) or with established knee osteoarthritis. The study participants were from Birmingham, Alabama and Iowa City, Iowa in the U.S. (14). The study started in 2003 when study participants were interviewed by telephone and attended clinic visits. Further details of inclusion and exclusion criteria have been published (14, 15). The initial visit included examination age, height, weight, self-reported physical activity level, knee extensor muscle strength, self-reported physical function and pain, radiographic evaluation, and Magnetic Resonance Imaging (MRI).

For this analysis we excluded those who had total knee replacement (TKR) at the baseline MOST visit, and any individuals who had total hip replacement (THR) at any time during MOST follow-up as these individuals may have had hip OA at baseline which affected the studied associations. We focused on persons with symptomatic OA at the baseline visit who had knee extensor strength measurements(2). Frequent knee symptoms were assessed by questionnaire; radiographic knee OA was assessed with fixed flexion posteroanterior (PA) and lateral weight-bearing radiographs. We defined symptomatic knee OA as present when the person reported frequent knee pain, aching or stiffness on most days when asked during their clinic visit and whose radiograph demonstrated Kellgren and Lawrence (K&L) grade 2 in any compartment in that knee(16). Subjects with bilateral OA or using assistive devices were included.

All measures are from the baseline MOST visit

Exposure: Knee extensor muscular strength

Concentric isokinetic strength of the quadriceps knee extensor was measured using a Cybex 350 isokinetic dynamometer at 60°/sec. After instruction, and 3 practice trials, participants completed 4 repetitions; peak torque over 4 repetitions was used for concentric knee extensor strength (2). Strength from the “worse knee” by K&L score was used as a continuous variable (strength in Nm). Secondary analyses used the ratio of strength (Nm) and body weight (kg) (17, 18) as the exposure.

Measures of physical function

Measures of physical functional described below chosen for this analysis involve employment of quadriceps strength to move the body in opposition to gravity: rising from a chair, going up stairs, getting on and off the toilet, and included the major functional activity of walking.

20-Meter Walk Test: We measured total time in seconds for study participants to walk at their usual walking pace from the starting point to the end. The test was then repeated, and we used the mean time of the two test trials, in seconds. Refusal or inability to do the test, or use of walking aids were recorded.

Five Times Sit-to-Stand Test: Using a chair with a straight back; flat, level and firm seat; and seat height 45 cm at front, participants stood up from the chair five times as quickly as they could, keeping their arms folded across their chest. Walking aids were not allowed. Refusal or inability to do the test were recorded. We recorded total time in seconds using a stopwatch from start to finish of the test; the test was then repeated, and we used the mean time of the two test trials, in seconds.

Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC): We chose 3 individual questions from the WOMAC survey which use quadriceps strength and are similar to the performance-based measures: going up stairs, rising from a chair, and getting on or off the toilet. For each of these outcomes, respondents answered a question “How much difficulty have you had...” performing the task. For each question, possible responses were “none” (scored 0, best performance level), “mild” (1), “moderate”(2), “severe”(3), or “extreme” (4 - worst performance level), yielding an ordinal value ranging 0–4 for each WOMAC item outcome.

In addition for each WOMAC outcome we created a dichotomous variable which classified individuals as having a “High level of difficulty” with the task (combining “2-moderate”, “3-severe”, and “4-extreme”) or a “Low level of difficulty” (combining “0-none” and “1-mild”). The dichotomization of this measure made it easier to explain, and divided subjects into High and Low categories near the median number of respondents.

Covariates

Age: Age in years was used as a continuous variable.

Weight: Weight in kilograms at baseline was used as a continuous variable.

Statistical Methods

We took an exploratory and graphical approach to identify inflection points, or thresholds, in the relationship between measures of physical function and quadriceps strength. We stratified by sex due to differences in the distributions of strength and height in men and women. Our primary analyses adjusted for age, and weight, which have been linked to performance in other studies of function(6, 8, 9, 19). Analyses were performed using SAS software version 9.4.

Participant characteristics were summarized with frequencies and means. For continuous outcomes 20-Meter Walk, and the Five Times Sit-To-Stand Test, we graphically explored the shape of the relationship between quadriceps strength and each outcome using nonparametric locally weighted regression scatterplot smoothers (LOESS)(20), separately for men and women, seeking possible inflection points which might indicate a threshold of strength that alters the relationship with physical function. A range of potential inflection points around the value suggested by inspection of the graphs were then fit in separate piecewise models(21) and tested with nonlinear least squares regression for convergence to a solution which best fit the data. We limited points to those between the 20th and 80th percentiles of strength for stability of the models. Our primary models used strength as the exposure, adjusted for age and weight; major differences in height were already addressed by stratification by sex. While we report p-values examining the change in slope below and above the specific inflection points tested, these were considered exploratory aids to guide selection of points, and not definitive tests of the exact locations. Using these selected inflection points as fixed quantities in a regression model, the change in slope was tested to see if it was non-zero, using an F-test.

For WOMAC outcomes we used proportional-odds logistic regression with restricted cubic splines to evaluate non-linear relationships with quadriceps strength(22). A range of potential inflection points around the point(s) suggested by the cubic spline model(s) were fit using piecewise linear trends in the log odds using separate logistic regression models. The $-2 \text{ Log Likelihood}$ was used to aid in the selection of an inflection point between the 20th and 80th percentiles of strength, and then the change in slope was tested using a chi-square test in the proportional odds regression model with the fixed inflection point.

In secondary analyses for the performance-based outcomes, we tested a set of models using the ratio of strength and weight (i.e. normalized strength) as the exposure, first stratified by sex and adjusted only for age; then using the sample of men and women together and adjusted for age and height. The ratio “strength/weight” (Nm/kg) is less interpretable than “strength”, but accommodates different ranges of strength and/or weight: men and women may have the same ratio, but very different strength and weight values.

RESULTS

The 834 study participants (Figure 1), were on average 62.9(\pm 7.9) years of age, with mean BMI 33.1(\pm 7.1) kg/m², and 65.8% female (Table 1). All participants had symptomatic OA in at least one knee, with 64% of both men and women having a maximal K&L score in the

worse knee of 3 or 4. Mean quadriceps strength in women ($52\pm 23\text{Nm}$) was lower than in men ($105\pm 39\text{Nm}$).

Results in Women

In women, the LOESS plot for the performance-based 20-meter Walk Test vs. quadriceps strength (figure 2) suggested the presence of an inflection point in strength near 60 Nm. In a piece-wise linear model the slope of strength versus walking time became steeper at quadriceps strength of 56.8Nm (slope before 56.8Nm = -0.11 , slope after 56.8Nm = -0.02 , p-value = 0.001 for difference in slopes), indicating a steeper relation of strength with elapsed walking time below this threshold in women.

The LOESS plot for Chair Stand Test results versus quadriceps strength (figure 3) suggested an inflection point below 50Nm; in a piece-wise linear model we found the slope of strength vs. chair stands time became steeper at strength 32Nm (slope1 = -0.30 , slope2 = -0.05 , p-value < 0.0001 for difference in slopes). LOESS analyses using strength/weight as the predictor showed similar graphical relationships.

In unadjusted proportional odds models with restricted cubic splines, we found evidence of non-linearity in the association of strength and the WOMAC items “rising from a chair” and “getting on and off the toilet” in women (graphs not shown). The joint effect of nonlinear components in the restricted cubic spline models for “rising from a chair” was of borderline significance (chi-square = 5.99 , d.f. = 2 , p = 0.05), and became non-significant after adjustment for age and weight (chi-square = 5.13 , d.f. = 2 , p = 0.08). For “getting on and off the toilet” neither association was statistically significant (unadjusted: chi-square = 4.95 , d.f. = 2 , p = 0.08 ; adjusted: chi-square = 4.49 , d.f. = 2 , p = 0.11). For WOMAC “going up stairs” we found no significant evidence of non-linearity in the restricted cubic spline models (p = 0.23 in age and weight adjusted models).

In explorations of piece-wise models in individual WOMAC items in women (figure 4), we found suggestions of an inflection point in quadriceps strength at around 38Nm for both difficulty “rising from a chair” (slope1 = -0.034 , slope2 = -0.024 , p-value = 0.12 for difference in slopes) and “getting on and off the toilet” (slope1 = -0.038 , slope2 = -0.029 , p-value = 0.05 for difference in slopes). After adjustment for age and weight, the changes in slope were reduced (“rising from a chair” slope1 = -0.031 , slope2 = -0.019 , p = 0.20 ; “getting on and off the toilet” slope1 = -0.035 , slope2 = -0.023 , p = 0.11). The association of quadriceps strength and difficulty “going up stairs” (figure not shown) appeared to be linear; we found no suggestion of inflection points between the 20th to 80th percentiles of strength in women (highly non-significant p-values > 0.37 for tests of inflection points at 33 through 87Nm of strength in women).

Results in Men

Men had a wider range of strength values than women (Table 1). For men the LOESS plots and models for walking time (Figure 2) and chair stands time (Figure 3) suggested approximately linear relationships between quadriceps strength and these outcomes. In men, piece-wise linear models suggested no inflection points for walking time or chair stands time

in the 20th to 80th percentile range of strength. Mean walking time for the 20-meter test was faster than 1.0 meter/second for all men in this sample.

In men, restricted cubic spline models yielded no suggestions of non-linearity in the association of quadriceps strength and the WOMAC items (tests of joint effect of nonlinear components in adjusted models: for “going up stairs”, “rising from a chair” and “getting on and off the toilet”, $p=0.20, 0.39, \text{ and } 0.75$, respectively). In explorations of piece-wise models for individual WOMAC items (figure 4) we found no visual evidence of inflection points in the range 20th to 80th percentiles of strength in men, with non-significant p -values for tests of inflection points at 73 through 134Nm of strength.

Secondary Analyses

In secondary analyses using normalized strength as the exposure (i.e. the ratio of strength/weight), in men and women together, for the 20-Meter Walk Test the estimated inflection point was 0.74 Nm/kg (slope1= -8.761 , slope2= 7.757 , $p<.0001$ adjusted for age and height). Of 494 individuals with a strength/weight ratio below 0.7432 Nm/kg, 83% were women, 17% men. Reviewing the characteristics of individuals with a strength/weight ratio of $< 0.74\text{Nm/kg}$, we found women in that range had a mean strength of 42Nm, well within the 20th to 80th percentiles of strength in women. Men had a mean strength of 58Nm in that range, below the 20th percentile of strength in men. Only 22 men were below the inflection point for the ratio, but above the 20th percentile in strength for men.

For tests of Chair Stand Time with normalized strength, in men and women together, the estimated inflection point was 0.30Nm/kg (slope1= -37.274 , slope2= 33.269 , $p<.0001$ adjusted for age and height). However, the mean strength of individuals with that ratio of strength/weight is not above the 20th percentile of strength for either men or women.

DISCUSSION

In this study of persons with knee OA, we found suggestions of strength inflection points in associations between quadriceps strength and physical function measures in women, but not in men. If these cross sectional data are applicable to treatment effects, they suggest that rehabilitation strategies that focus on strengthening are likely to be more effective in improving function in women who are weaker than those who are stronger, including men. For those above the inflection point, our results may provide an incentive to maintain those higher levels of strength. The results also suggest that a quantitative assessment of strength might be indicated prior to rehabilitation planning.

Analyses focused on common functional tasks that require quadriceps strength, arising from a sitting position and going up stairs. Walk time was included because it is one of the most commonly evaluated measures of physical performance(23). Strength inflection points in women were in the vicinity of 57 Nm for the 20-meter walking speed test, and 32 Nm for the Five Times Sit-to-Stand Test. In concordance with the Sit-to-Stand Test results, we found suggestions of strength inflection points near 38Nm for WOMAC items involving similar physical actions: “rising from a chair”, and “getting on and off the toilet”. For women, these strength estimates were close to the median value of 52Nm, and the cutoff for the lowest

quintile of 33Nm respectively. These values provide thresholds in the sense that for knee extensor strength values above the threshold, the relationship between function and strength increased more slowly, but we did not find thresholds where the relationship “flattened out” with no improvement in function above the threshold value. A comparison may serve to contrast relationships below or above the strength inflection point estimated for 20-Meter Walk Time. Our model estimates that for a 20% increase in strength for persons whose strength fell below the inflection point, the improvement in walking time was nearly a second (for strength 40Nm and 48Nm, predicted walking times are 19.8 and 18.9 seconds respectively), while for those above the inflection point, a 20% increase in strength resulted in a 0.23 second faster walk time (for strength 60Nm and 71Nm, predicted walking times were 17.7 and 17.5 seconds respectively.).

We have estimated the location of inflection points using visual and exploratory methods. While we are confident that these inflections occur close to the strength values presented here, the exact placements are likely different from our values. The p-values used for testing individual threshold values suffer from a multiple testing problem, and small differences in thresholds would be very challenging to detect even with very large observational datasets.

Our findings are similar to other studies exploring thresholds of strength and function, that have not focused on persons with arthritis (6, 8–10, 24–26). In a population-based sample of older women with significant functional limitations, Ferrucci et al. (9) found largely non-linear associations between both hip flexor and knee extensor muscle strength and performance-based tests of walking speed, chair stands, and standing balance. Another study in community-dwelling women found thresholds of quadriceps strength below which performance of basic ambulatory tasks (gait speed, chair rise, stair ascent and descent) was likely to be compromised (26).

Our findings, while cross sectional and not examining treatment effects, have important implications for rehabilitation strategies. Identification and use of functionally relevant thresholds of quadriceps strength enables both the identification of appropriate patients and therapeutic guidance for rehabilitation interventions with the goal of preserving physical function in people aging with knee OA. Knowing the specific targets for strength that may prevent or delay disability in women with symptomatic knee OA advances our ability to provide strengthening interventions most likely to result in clinically meaningful functional improvement. For those whose strength is below the identified thresholds, strengthening interventions may improve functional performance on relevant tasks such as getting out of a chair and ascending stairs, while for those who are not weak and who are struggling with these functions, other rehabilitation interventions with less focus on strengthening, e.g. weight management, or attention to flexibility, or balance, may be preferred. This stratification of patients echoes personalized medicine approaches and would be consistent with arguments favoring phenotype differences among OA patients (27–29) that would motivate different treatment approaches.

While our data suggest thresholds of strength in women below which the strength function relationship is steeper, we found no such thresholds in men who were in general much stronger than women(30, 31). This sex difference is likely because a certain threshold of

strength is needed to carry out these particular tasks and few men fell below this threshold. Therefore, we lacked statistical power to evaluate this relationship. In secondary analyses using the ratio of strength/weight as the exposure, for the 20-Meter-Walk Test, only 17% of the individuals with the estimated ratio 0.74 Nm/kg were men. Men, and stronger women, may encounter thresholds with more difficult tasks, which were not included in this study.

The MOST data set has several key strengths for this type of analysis. MOST is a community sample that did not select persons with OA based on the severity of disease. Participants in this sample were chosen to mirror a typical clinical situation in which patients with knee OA may be referred to physical therapy for strengthening. Although many individuals in this sample had advanced OA by K&L grade (Table 1) in the worse knee, this should still be broadly representative of OA severity in the community, and therefore be representative of those seeking rehabilitative treatment for OA. Knee extensor strength was measured using an isokinetic dynamometer, measuring knee strength while the leg is in motion, rather than pressing against a static instrument. We included both men and women, and as all participants had some level of osteoarthritis, they represent a sample that is neither severely disabled, nor extremely healthy, but rather span a range of performance.

A limitation of this analysis is that it is cross-sectional, although one might argue that effects of strength on function should be immediate. This is not a treatment study, so the effectiveness of strengthening at different levels of advanced disease can not be predicted. In addition, it is possible that control for other factors which affect function, such as pain, other muscle involvement, medical conditions, or psycho-social factors would diminish the association of quadriceps strength with function, although it is likely to still be a major contributing factor for physical function.

Future studies should evaluate longitudinal associations of changes in strength and changes in function, exploring whether inflection point(s) which appeared for some outcomes in this cross-sectional analysis are present in longer-term analyses – e.g. do weaker women (below the threshold at baseline) have different response over time compared to stronger women, or men? Future analyses should include individuals without osteoarthritis, and explore the role of other factors besides quadriceps strength which may affect function, such as pain, hip or other muscle strength, other medical conditions, or psycho-social factors such as self-efficacy or depressive symptoms, as this may aid in tailoring rehabilitation programs as well. More difficult or strenuous measures of function, and endurance, should be evaluated to investigate other potential thresholds of strength which may occur in stronger individuals.

In summary, the major finding of this study in persons with knee OA is evidence of strength thresholds in several basic functional tasks, such as rising from a chair, in women, but not in men. Although other factors also affect physical function capabilities, these thresholds in strength may provide a means of identifying individuals at the brink of disability, insofar as the contribution of quadriceps strength to basic functional tasks in daily life. These individuals may benefit most from strengthening interventions.

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SIGNIFICANCE AND INNOVATIONS

- We explored quadriceps strength and physical function in individuals with knee osteoarthritis (OA) from the Multicenter Osteoarthritis Study (MOST).
- We found evidence of strength thresholds for functional tasks which involve the body acting against gravity, such as walking, or rising from a chair, in women but not in men.
- These thresholds in strength may provide a means of identifying individuals at the brink of disability, for whom increments in strength may be associated with improvements in physical function or greater ease in carrying out common tasks in daily life; for individuals above the strength threshold, focus should be on maintaining strength.

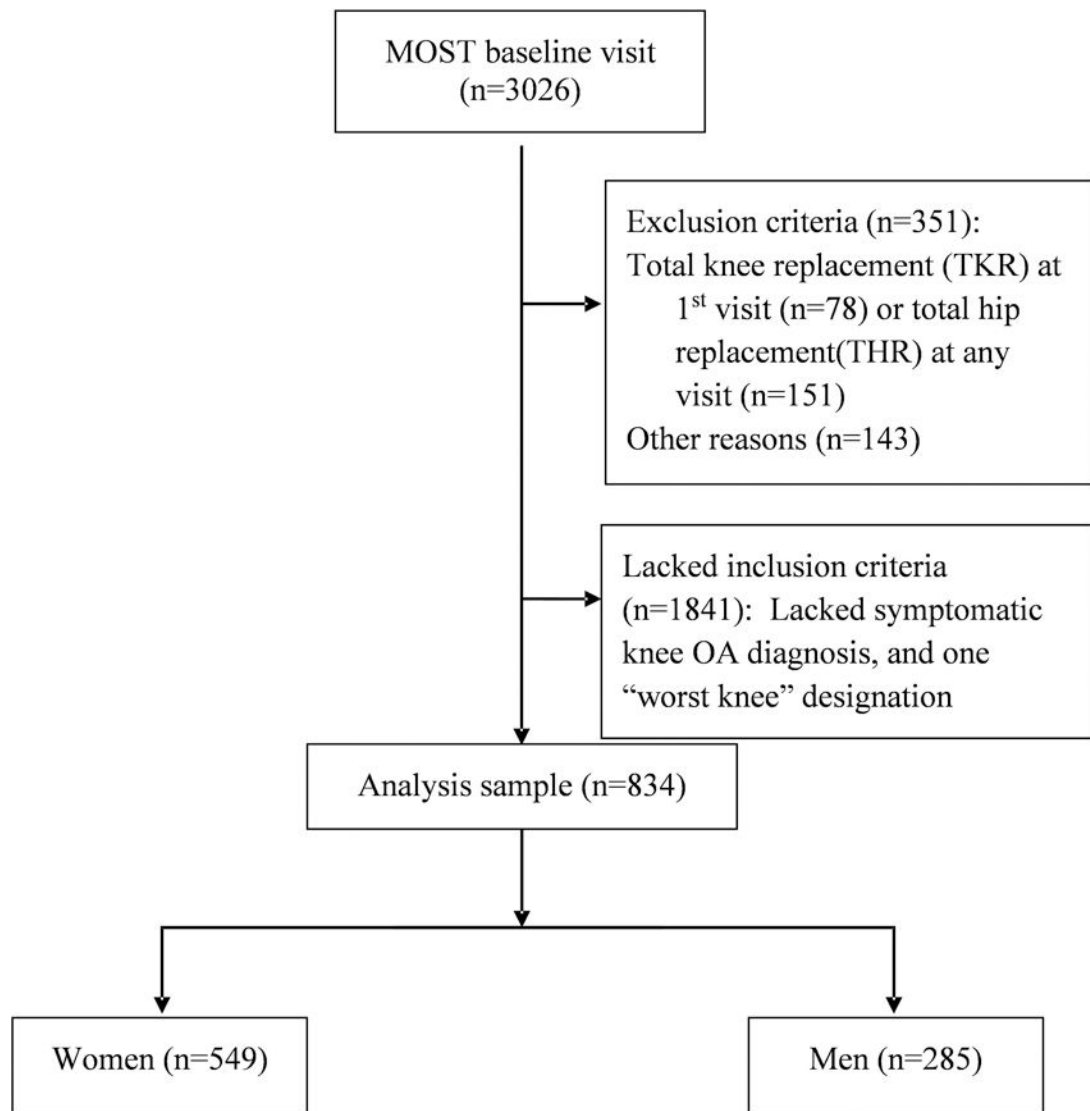


Figure 1.
Analysis Sample Flow Diagram.

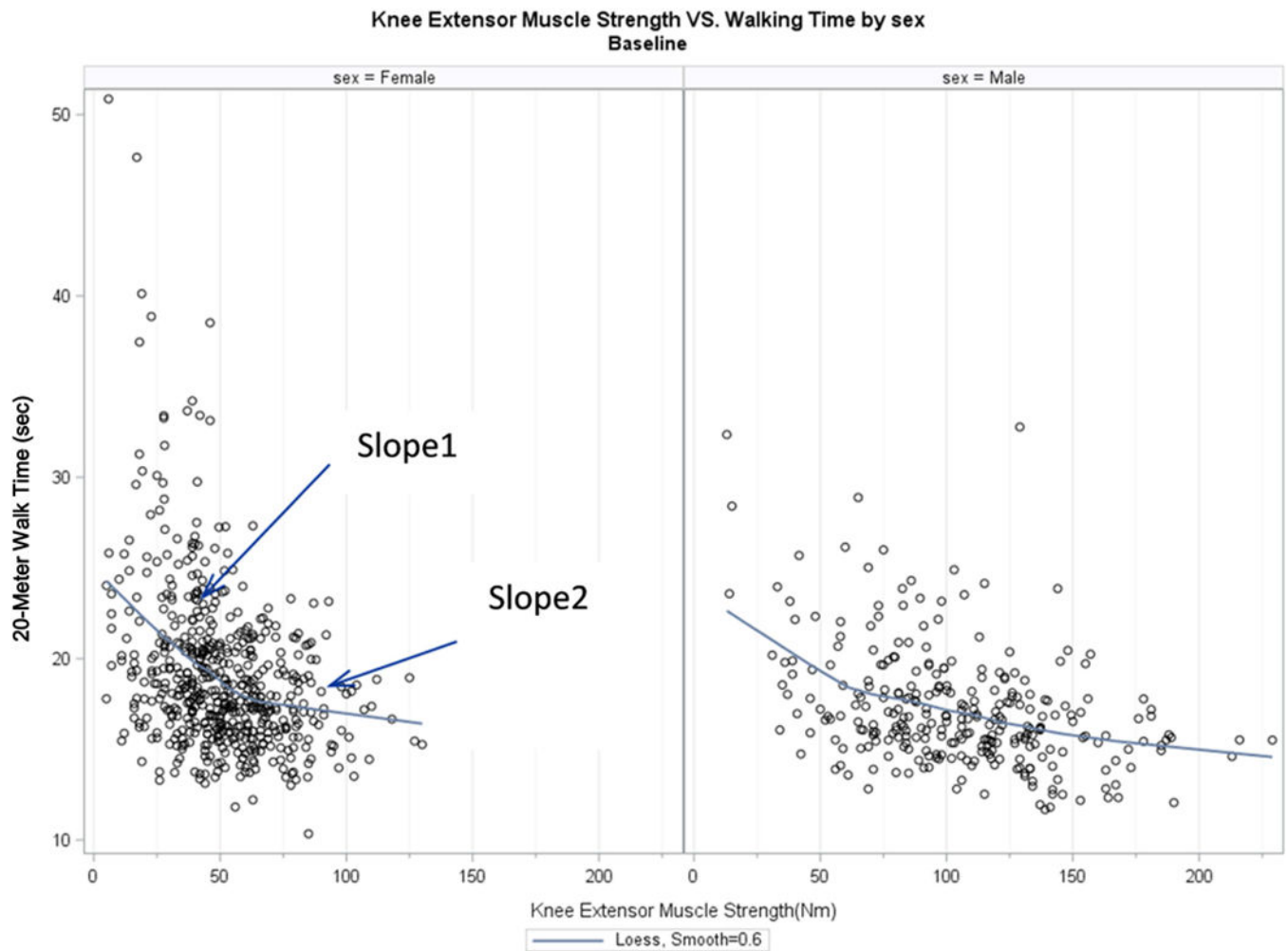


Figure 2.

Knee Extensor Muscle Strength vs. 20-Meter Walk Time, by sex. Nonparametric local weighted regression (LOESS) was used to generate the scatter plots and LOESS lines. In women the piece-wise linear model indicated a possible inflection point at 56.8Nm (arrows indicate segments of the LOESS line: slope1= -0.11 , slope2= -0.02 , p-value for difference in slopes= 0.001). In men no inflection points were found in the 20–80% range of strength.

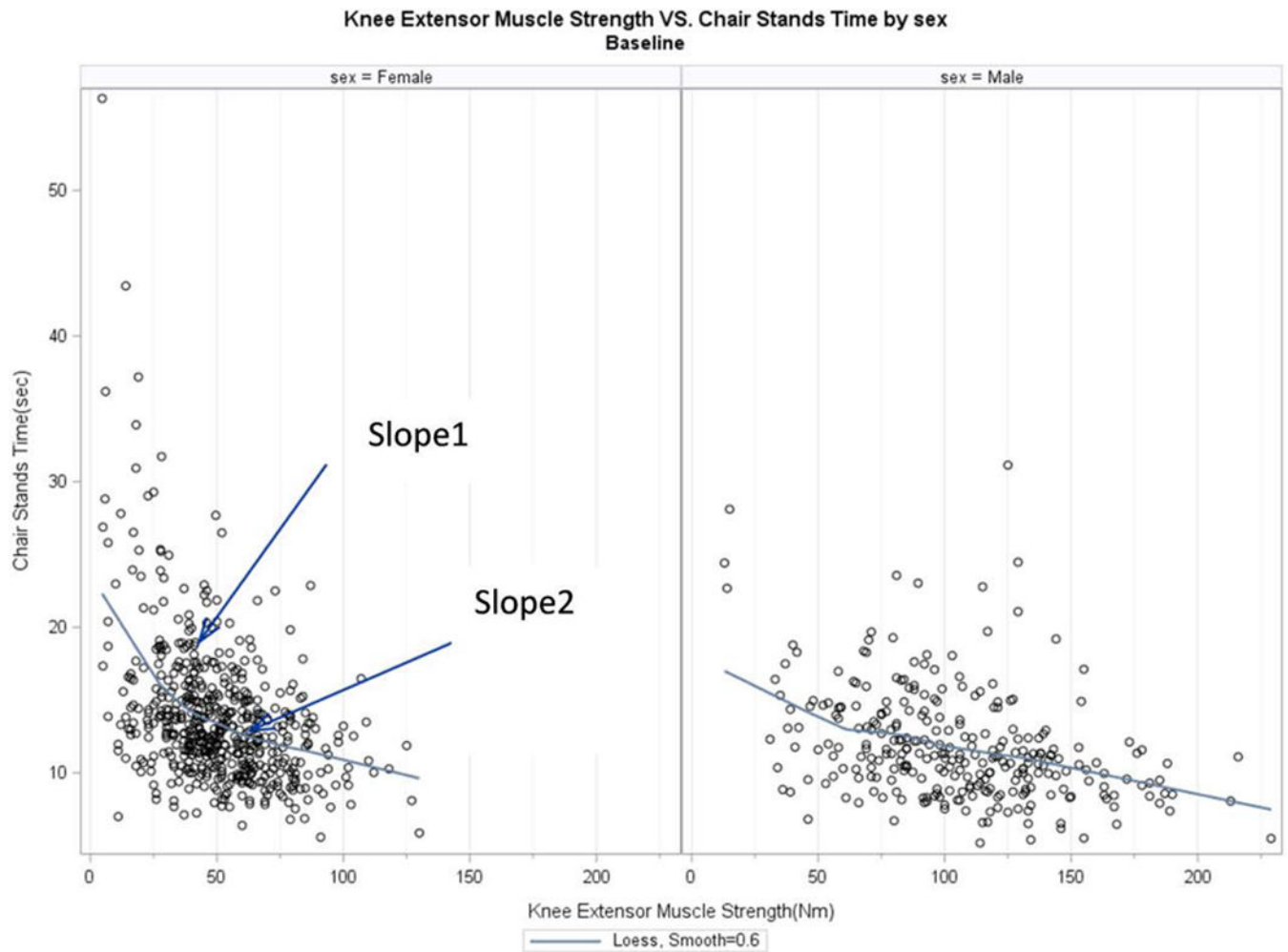


Figure 3.

Knee Extensor Muscle Strength vs. Chair Stands Time, by sex. Nonparametric local weighted regression (LOESS) was used to generate the scatter plots and LOESS lines. In women the piece-wise linear model indicated a possible inflection point at 32Nm (arrows indicate segments of the LOESS line: slope1= -0.30 , slope2= -0.05 , p-value for difference in slopes <0.0001). In men no inflection points were found in the 20–80% range of strength.

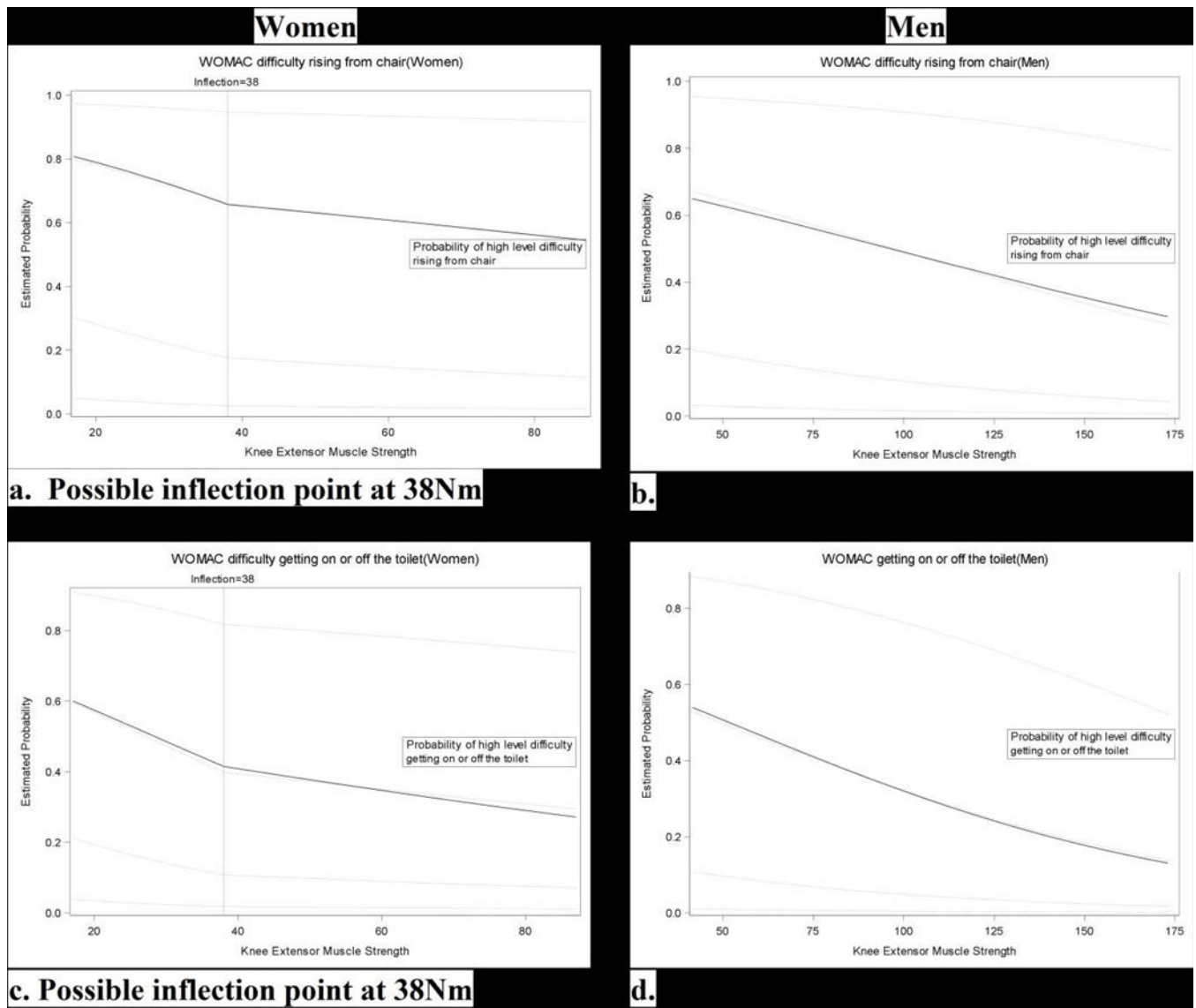


Figure 4. Estimated probabilities for association of quadriceps strength and selected WOMAC items from logistic piece-wise regression models. Figures show estimated probabilities for the association of strength and each WOMAC item. Graphs combine both ordinal and dichotomous WOMAC outcomes variables, from unadjusted models. Plots are restricted to 5–95% range of strength distribution by sex. Possible inflection points of strength are noted on graphs, where found. Dark lines: probability of “high level of difficulty” for dichotomous WOMAC outcomes (combining WOMAC Extreme, severe, or moderate level of difficulty). Dotted lines: ordinal WOMAC variable probabilities.

Table 1.

Sample Baseline Characteristics

		Males n=285 (mean, sd)	Females n=549 (mean, sd)
Age		62.5(8.3)	63.1(7.7)
Weight (kgs)		101.7(21.7)	89.1(20.2)
BMI: Body mass index (KG/M**2)		32.2(6.5)	33.5(7.3)
KL Grade (baseline, worst Knee)	Grade 2	26%	36%
	Grade 3	42%	43%
	Grade 4	32%	21%
Knee extensor muscle strength (Nm) (m,sd)		105.3(38.7)	51.5(22.8)
Cutoffs for quintiles of strength(Nm)	Q1	< 73	<33
	Q2	73 – 92	33–43
	Q3	93 – 113	44 – 53
	Q4	114 – 133	54 – 66
	Q5	>=134	>=67
Normalized Strength (Strength/Weight Ratio, Nm/kg)		1.1(0.4)	0.6(0.3)
<i>Performance-based outcomes</i>			
Chair stands (5 chair stands, average time in seconds)		11.9(3.9)	13.8(5.2)
Walking time (20-meters, average time in seconds)		17.2(3.3)	19.3(5.7)
<i>WOMAC self-reported outcomes</i>			
Going up stairs? (% High difficulty)		55%	70%
Rising from sitting position?(% High difficulty)		48%	64%
Getting on or off the toilet?(% High difficulty)		33%	40%

NOTES: Normalized strength (Nm/kg) is used only in secondary analyses.

WOMAC questions are for either knee, in the past 30 days, dichotomized as High level of difficulty, vs. Low level of difficulty with this task.