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Identifying participants with knee osteoarthritis likely to benefit from physical therapy education and exercise: A hypothesis-generating study

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Background: The purpose of this investigation was to undertake a hypothesis-generating study to identify candidate variables that characterize people with knee osteoarthritis who are most likely to experience a positive response to exercise.

Methods: One hundred fifty participants with knee osteoarthritis participated in this observational, longitudinal study. All participants received a standard exercise intervention that consisted of 20-minute sessions two to three times a week for three months. The classification and regression tree methodology (CART) was used to develop prediction of positive clinical outcome. Positive pain and disability outcomes (dependent variables) were defined as an improvement in pain intensity by >50% or an improvement of five or more on the Oxford knee score, respectively. The predictor variables considered included age, sex, body mass index, knee osteoarthritis severity (Kellgren/Lawrence grade), pain duration, use of medication, range of knee motion, pain catastrophising, self-efficacy and knee self-perception.

Results: Fifty-five participants (36.6%) were classified as responders for pain intensity and 36.6% were classified as responders for disability. The CART model identified impairments in knee self-perception and knee osteoarthritis severity as the discriminators for pain intensity reduction following exercise. No variables predicted reduction of disability level following exercise.

Conclusions: Such findings suggest that both body perception and osteoarthritis severity may play a role in treatment outcome with exercise. It also raises the possibility that those with higher levels of disrupted body perception may need additional treatment targeted at restoring body perception prior to undertaking exercise.

Significance:

Regardless of other variables including age, sex, body mass index, pain duration, use of medication, knee range of motion, pain catastrophising and self-efficacy, participants with knee osteoarthritis who report low levels of body perception disruption (a FreKAQ score ≦ 17) and minimal structural changes (KL grade I) demonstrate significantly better outcomes from exercise therapy than other participants.

Identifying participants with knee osteoarthritis likely to benefit from physical therapy education and exercise: a hypothesis-generating study

Running head: Knee osteoarthritis benefit from exercise

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1. Introduction

Knee osteoarthritis (OA) is a common diagnosis in the adult population and often results in pain and functional disability (Bijlsma et al., 2011). Although exercise is a recommended first-line treatment (Roos, & Juhl, 2012), systematic review evidence suggests that exercise has only moderate effects on both pain and function (Fransen et al., 2015). One explanation for the modest effect sizes may be the clinical complexity and heterogeneity of people with OA associated knee pain (Sinikallio et al., 2014). While radiological evidence of degeneration is a sentinel feature of knee OA, such findings are highly prevalent in pain free individuals (Horga et al., 2020) and the degree of structural change is not strongly associated with levels of reported pain (Bedson, & Croft, 2008), suggesting that other factors require consideration. For example, people with higher Body Mass Index (BMI) experience greater pain than individuals with lower BMI even when taking into account OA severity (Weiss, 2014). Further, increased pain at one year follow up has been associated with worsening of disability at three years (van Dijk et al., 2010) and baseline knee extension range has been shown to be a predictor of lower limb functional performance (Pisters et al 2012). Systematic review data has demonstrated moderate evidence for a relationship between knee pain and cognitive factors including coping style, self-efficacy, somatisation, pain catastrophization and helplessness (Urquhart et al., 2015). Furthermore, preliminary data indicates that self-reported disturbed body-perception is also associated with clinical status in people with knee OA (Nishigami, et al., 2017). These clinical characteristics may need to be integrated into the clinical reasoning process when delivering physical therapy care.

Various strategies have been proposed to assist with clinical reasoning; one popular approach is the use of Clinical Prediction Rules (CPRs). CPRs are data-generated tools designed to help inform clinical decision making around issues of diagnosis, prognosis and treatment selection (Cook, 2008). Prescriptive CPRs refer to those associated with treatment selection and are used to help inform treatment decision making by identifying the characteristics of patients with a greater likelihood of treatment response to a given intervention (Cook, 2008). Many studies have evaluated prognostic factors of the long-term clinical course of knee OA in general practice. These studies found that factors such as age, BMI, physical impairment measures and psychosocial factors hold prognostic value for knee OA (Alschuler et al. 2013; Belo et al. 2009; Holla et al. 2010; Holla et al. 2014; Kastelein et al. 2016; Van Dijk et al. 2010). To date, only one CPR study from the knee OA literature sought to identify characteristics of people with knee OA who respond favorably to a specific treatment, in this case hip joint mobilization (Currier et al., 2007). However, pain-related assessments were not fully examined in this study, the follow up period was only two days and the treatment investigated is not clearly part of evidence based guidance (McAlindon TE et al., 2014). We are unaware of any attempt to identify predictive factors specific to response to guideline informed education and exercise therapy in knee OA. Development of CPRs for identifying participants with knee OA who are likely to respond to education and exercise interventions may improve clinical decision-making and the treatment success rate.

The first step in creating a CPR is to undertake hypothesis generating research. In hypothesis generation, the predictive value of certain factors are explored using an observational cohort study design in which all participants are provided with the intervention of interest (i.e., education and exercise). This design allows for generation of predictive factors that are potentially related to treatment outcome and thus, factors that may be relevant to test in a larger randomised controlled trial (RCT) that utilizes treatment effect modification analyses (i.e., the analysis needed to effectively evaluate CPRs). Therefore, here we aimed to determine factors that identify participants with knee OA most likely to experience a positive response to education and exercise.

2. Methods

The study was conducted after obtaining approval from the Kyushu Medical, Orthopedic Surgery, Internal Medicine and Rehabilitation Clinic Ethics Review Committee (approval number: 20160606). Written, informed consent was obtained from all subjects prior to the study. The study was conducted in compliance with the Declaration of Helsinki.

2.1 Participants

People with symptomatic knee OA who were newly referred for physical therapy at 14 hospitals or medical clinics were considered for inclusion in this study. Recruitment took place between April 2017 and September 2018. All patients underwent an X-ray examination and were screened for eligibility by orthopedists. Inclusion criteria were as follows: adults with radiographic knee OA (a score of at least one on the Kellgren/Lawrence scale (KL scale)); aged between 50-90 years of age; experiencing current knee pain during motion of $\geq$ 2 on an 11 point numerical rating scale (NRS), or with disability scores less than 43 on the Oxford Knee Score (OKS; lower scores representing higher disability). People were excluded if they had previous total knee arthroplasty on the same or opposite side, serious knee pathology (unhealed fractures, tumors, acute trauma), significant illness that precluded exercise, including the presence of dementia, previous stroke, neuromuscular disease, and psychiatric illness as diagnosed by a psychiatrist. Participants who reported severe, uncontrolled pain at a site other than the knee were also excluded to avoid significant pain in other parts of the body impacting on self-reported disability. We operationalized this by excluded participants who answered yes to the question "Do you have any other pains that interfere with your daily life?"

2.2 Dependent variables

Pain intensity during movement was measured using a 0-10 numeric rating scale anchored at the left with "0 = no pain" and at the right with "10 = unbearable pain" in reference to the following question, "What is the intensity of your knee pain with movement?" Knee-specific disability was evaluated using the OKS, a valid, reliable, and responsive measure of functional disability (Dawson et al., 1998). An overall score (out of 48) is calculated by totaling responses to 12 questions, each with five potential Likert-type responses (e.g, 0 = total disability to 4 = no disability). Higher scores represent lower levels of disability. At baseline, the NRS and OKS were measured in all patients. Each participant completed the NRS and OKS assessment again after the three month education and exercise program.

2.3 Measurement of potential predictor variables

Age, gender, BMI, pain intensity during movement, severity of radiographic changes (KL grade), pain duration, medication use, knee joint extension range of motion, pain-related catastrophizing, pain-related self-efficacy, and knee-specific body-perception were assessed in all participants at baseline. Pain was graded as mild (score 1-4), moderate (score 5-7), or severe (score 8-10) (Kapstad H et al., 2008). Antero-posterior and lateral radiographic images were recorded with participants positioned in supine. Severity of degenerative knee OA changes was evaluated using the KL scale by experienced orthopedists blinded to the patient's clinical condition. The KL scale ranges from 0 - IV with higher numbers indicating increased severity of OA (Kellgren, & Lawrence, 1957). Participants were also coded as to whether they were taking non-steroidal anti-inflammatory drugs (NSAIDs) or not at intake as the use of NSAIDS has been shown to be predictive of pain improvement at three months in people with knee OA (Snijders et al., 2011), Pain-related catastrophizing was measured using the Japanese version of the Pain Catastrophizing Scale (PCS) (Matsuoka, & Sakano, 2007; Sullivan et al., 1995). The Japanese version of the Pain Self-Efficacy Questionnaire (PSEQ) was used to assess the confidence that people with knee pain have in performing activities while in pain (Adachi et al., 2014; Nicholas, 2007). Self-reported body-perception of the knee was evaluated using the Fremantle Knee Awareness Questionnaire (FreKAQ) (Nishigami et al., 2017). The FreKAQ is composed of nine items that relate to neglect-like symptoms, reduced proprioceptive acuity, and altered perception of body shape and size. Higher scores on the FreKAQ indicate more disturbed body perception.

2.4 Sample size

Ten to 15 subjects per potential variable are required to ensure an adequate sample size for the development of decision tree analyses (Glynn, & Weisbach, 2009; McGinn et al., 2000; Wasson et al., 1985). Eleven potential predictor variables were included within this study; hence, using this rule, a sample size of 110 to165 was required. NRS and OKS measures at three months were available for 150 subjects, which meets this criteria.

2.5 Intervention

The Template for Intervention Description and Replication checklist (Hoffmann et al., 2014) was used to guide the intervention description (Table 1). The primary aims of the program were to decrease pain and improve physical function. All participants received education regarding the etiology of knee OA, instruction on pain neurobiology and information on the benefits of exercise before commencing the exercise sessions. Participants were then orientated to a standardized exercise programme that including lower limb stretching exercises as well as both open and closed kinetic chain strengthening exercises for the lower limbs. Participants undertook the standard exercise programme for 20-minutes, two to three times a week for three months during individual outpatient sessions under the supervision of a physical therapist. The clinicians involved in the study had on average eight years' experience in the management of people with knee OA. The intensity of the exercises progressed over the treatment period, with the participants being encouraged to improve their capacity in the clinic and at home. If participants could complete two sets of 20 repetitions for the open chain strengthening exercise, they were instructed to progressively increase external load or add an additional set. Similarly for the squat exercise, once participants were able to perform two sets of 20 repetitions they were encouraged to add an additional set. Stretches were performed as three sets of 30 second holds for each muscle group and participants were encouraged to progress the stretch further into range over the treatment period. Participants were encouraged to perform the same exercises at home for three days per week followed by 20 minutes of continuous walking. The performance of home exercises was checked at each treatment session. Also, if participants reported excessive pain during the exercises, exercise levels were ceased or temporarily decreased and the physical therapist consulted about this at the next face-to-face session.

2.6 Statistical approach

All analysis was conducted by SPSS 24.0 (IBM, Tokyo, Japan). Student t-tests (continuous variables) and the chi-squared test (categorical variables) were performed to compare differences in predictor variables between dropouts and included participants, and between the responders and non-responders for both pain and disability. Changes in pain and disability from baseline to post-treatment were compared using a paired t-test. The significance level was set at $p \leq 0.05$. Effect sizes were calculated based on Glass'sΔ.

The classification and regression tree (CART) methodology, a decision tree model, was used to identify a common set of factors predictive of outcome (Breiman, Friedman, Olshen, & Stone, 2014). CART methodology is a common tool used in data mining that creates a model or algorithm that predicts the value of a target variable based on several input variables (Lewis, 2000). Each parent node in the decision tree produces two child nodes, which in turn can become parent nodes producing additional child nodes. This process continues with both tree building and pruning until statistical analysis indicates that the tree fits without overfitting the information contained in the data set. The CART method was used for the following two models. Model 1 utilized reduction of pain intensity as the dependent variable in which participants with a 50% reduction in pain intensity after three months were classified as responders (Chauny et al., 2014; Dworkin et al., 2005; Dworkin et al., 2008). Model 2 utilized improvement in disability as the dependent variable. Participants with a decrease in the OKS of five points or more at three months were classified as responders based on previous estimates of the Minimal Clinical Important Difference (MCID) for the OKS (Beard et al., 2015). In both models, the potential predictor variables were age, sex, BMI, pain intensity, KL score, pain duration, NSAIDs use or non-use, knee extension range, PCS scores, PSEQ scores and FreKAQ scores.

We evaluated sensitivity, specificity, positive likelihood ratios (LR+), negative likelihood ratios (LR-), positive predictive values (PPV), and negative predictive values (NPV) in each CART analysis to confirm accuracy of the final combinations acquired by the CART analyses. Accepted, minimal standards for the sensitivity of a screener are 70% (Glascoe, 2005; Vanderheyden, 2011). A 10-fold cross-validation of the decision tree was performed to confirm the misclassification risk of the CART model estimated for the entire sample and to cope with the overfitting and instability inherent to the decision tree.

Given that CART analysis involves hierarchical dependence (e.g., each subsequent predictor is dependent upon the branch of the variable above it within the analysis), logistic regression analyses (dependent variable of responder status) were also undertaken to evaluate the association between clinical outcome and predictor variables without this dependence. This helps determine the generalizability of predictor variables of clinical outcome when the entire sample is considered. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated using multivariate logistic regression analysis.

3. Results

Of the 325 patients who received a diagnosis of knee OA, 48 were excluded. The reasons for exclusion were: severe, uncontrolled pain at a site other than the knee (n=8); a stroke or other central nervous system disorders (n=5); dementia (n=9) and minimal current pain or disability (n =26). This left 277 eligible patients and of these, 150 subjects were able to be followed-up at three months after the initial evaluation (See Fig 1). Participant characteristics are summarized in Table 2. All subjects in this study had medial-type knee OA. Results evaluating differences in predictor variables between dropouts (n = 127 [46%]) and the participants for this study (n = 150 [54%]) are provided in Table 2. Analyses showed that the study dropouts were significantly younger and reported lower pain intensity, PCS, OKS and FreKAQ scores than did study participants (Table 2). Differences at baseline between pain responders and non-responders were seen for KL score, knee extension ROM, OKS, PSEQ and FreKAQ. These two groups also differed at follow up on pain intensity, PCS, knee extension ROM, OKS, PSEQ and FreKAQ (Table 2). Disability responders and non-responders differed at baseline on pain intensity and OKS. These two groups differed at follow up on pain intensity, OKS, PCS, PSEQ and FreKAQ (Table 2).

There were significant improvements in pain intensity (NRS mean difference = 1.7, 95%CI = 1.356 to 2.031, effect size = 0.87, $p < 0.001$,) and disability (OKS mean difference = -3.5, 95%CI = -5.095 to -3.132, effect size = 0.52, $p < 0.001$) after three months of education and exercise therapy (versus baseline).

3.1 Prediction of improvement in pain and disability

Fifty-five participants (36.6%) achieved a 50% pain intensity reduction at three months. Similarly, fifty-five participants (36.6%) achieved a clinically meaningful reduction in knee related disability, classified as a reduction of five points or more on the OKS. Thirty-three participants (22.0%) achieved clinically meaningful reduction in both pain intensity and disability.

The CART model identified that the FreKAQ score and KL grade were discriminators for meaningful pain reduction. The rate of positive response to treatment in participants with higher levels of body perception disruption (FreKAQ scores >17) was 18.8%. The rate of positive response to treatment for those with lower levels of body perception disruption (FreKAQ score ≦17) and higher OA severity (KL grade II, III, and IV) was 40.0%. Lastly, those with lower levels of body perception disruption (FreKAQ score ≦17) and lower OA severity (KL grade I) had the highest rate of positive response to treatment at 73.1% (Fig 2). The CART model algorithm had a sensitivity of 71.0%, specificity of 73.1%, LR+ of 2.63, LR- of 0.39, PPV of 92.6% and NPV of 34.5%. The cross-validated misclassification risk estimate for the decision tree was 0.393, and the standard error was 0.040, meaning that this classification tree analysis could predict 50% pain intensity reduction after exercise with an accuracy of 60.7%.

The CART model did not identify any baseline variables that predicted a clinically important change in disability (OKS).

Multiple logistic regression analysis showed that the ORs (95% CI) for participants with meaningful pain reduction were 1.70 (1.06-2.73) for KL scale and 1.09 (1.01–1.17) for FreKAQ score compared to participants with non-meaningful pain reduction. No baseline variable predicted a clinically important change in disability (OKS), consistent with what was seen for the CART analysis (Table 3).

4. Discussion

The CART analysis suggested that the FreKAQ and knee OA severity scores discriminated between those with and without pain intensity reduction following education and exercise, and that a high level of disrupted knee perception at baseline (≥ 18 on FreKAQ) was associated with not achieving clinically meaningful levels of pain reduction with education and exercise. The sensitivity, specificity, LR+ and LR- of this model meets acceptable values (Glascoe, 2005; Vanderheyden, 2011), indicating this model may be a reliable and useful algorithm to predict the effect of education and exercise therapy from data obtained at the initial assessment.

Previous research has shown that people with chronic OA related knee pain exhibit impairments in some of the mechanisms thought to be associated with body representation, including reduced tactile acuity (Stanton et al., 2013), poor implicit motor imagery performance (Stanton et al., 2013), and decreased proprioceptive acuity (Cammarata, & Dhaher, 2012; Chang et al., 2014). The FreKAQ was developed to assess self-reported body-perception specific to the knee in people with knee pain and is a more direct measure of the consciously felt body. The data reported here and our previous work with the FreKAQ (Nishigami et al., 2017) support the idea that disrupted body perception is a feature of the knee pain experience and has previously been shown to be associated cross-sectionally with both disability and pain intensity in people with knee pain (Nishigami et al., 2017). Furthermore, contemporary understanding of the pain experience place internally held models about the state and capacity of the body as central to the emergence of pain (Stanton et al., 2018), so it is plausible that disrupted body perception influences how readily the pain experience is resolved with treatment. The present data supports this by suggesting that body perception disruption mediates the response to guideline based care for knee OA. In cases with high levels of disturbed body perception, 81% reported insufficient improvement of pain, whereas for those with a FreKAQ score below eighteen this figure dropped to 50%, though this effect is further influenced by the extent of radiographic changes. The clinical implications of this finding are that education and exercise interventions for people with demonstrated evidence of disrupted body perception might need to be complimented with interventions that particularly target this impairment. This might include such things as visuotactile illusions that alter perceived knee size, which have been shown to decrease knee pain for patients with knee OA (Stanton et al., 2018).

People who both scored ≦ 17 on the initial FreKAQ and had a KL grade of I were shown to be the most likely to experience pain relief with education and exercise. This is at least partially consistent with previous work showing that exercise may be more beneficial (versus invasive treatments such as intra-articular glucosamine injection) in those with early OA than those with advanced OA (Kawasaki et al., 2009). While high-level evidence supports that people with knee OA benefit from exercise regardless of their OA severity (Wallis et al., 2014), the current study extends past work by showing that standard physical therapy is more effective for patients with early OA changes when there is less evidence of disrupted body perception. However, given the lack of a control group, we cannot rule out that lower levels of disrupted body perception (FreKAQ) and low severity of OA (KL grade I) are prognostic factors rather than treatment effect modifiers.

Our data d o suggest that in patients who have lower levels of body perception disruption (≦ 17 on the FreKAQ), OA severity (KL grade I vs KL grades II-IV) appears to play a role in determining outcome. Of those with lower disruption of body perception and higher levels of OA severity (KL grade II, III or IV), only 40% had sufficient improvement of pain (60% did not), whereas in those with less severe OA (KL grade I), 81.2% had a sufficient pain improvement (18.8% did not). Previous work in people with moderate to severe knee OA has shown that OA severity (as assessed by MRI) does not predict response to exercise, with the exception of patellofemoral changes (severity of abnormalities in cartilage integrity and osteophyte formation) (Knoop et al., 2014). This raises several possibilities. First, our participants with higher KL grades may have also had patellofemoral changes which would predict a reduced response to exercise. Or second, KL grade may also be a corollary of other symptoms such as fear of movement (Somers et al., 2009), which may be supported by patient knowledge of the degree of 'joint damage' (e.g., bone-on-bone) (Holden et al., 2012), which then may result in reduced engagement in exercise interventions (Larsson et al., 2016). Such possibilities remain speculative as these measures were not captured in the present study. Last, KL grade II or higher is a common inclusion criterion of many exercise studies (for example, see Juhl et al., 2014), however, the present study also included people with KL grade I OA. In the present study, there were also no differences between KL grades II, III and IV for response to exercise which is largely consistent with previous results. Thus, it may be the recruitment of participants with mild OA (KL grade I) that influences the current findings.

It is interesting that despite the number of predictor variables considered, pain relief following education and exercise was only predicted by body perception and knee OA severity. Although a recent systematic review demonstrated that baseline knee pain intensity predicted the deterioration of knee pain and physical functioning (de Rooij et al., 2016), we did not find that baseline pain intensity predict the effect of education and exercise on these outcomes. Similarly, while NSAID use is predictive of pain improvement at three months in people with knee OA only receiving NSAID treatment (Snijders et al., 2011), – our results suggest that NSAID use does not enhance education and exercise related clinical outcomes. In addition, psychological factors such as pain catastrophizing and self-efficacy have been implicated in shaping pain and disability in patients with knee OA, and the need to intervene in these factors to prevent chronic pain has been suggested (Sinikallio et al., 2014 Hermsen et al., 2016). However, pain catastrophizing and pain self-efficacy were not identified as predictors of those participants with knee OA most likely to experience a positive response to education and exercise over three months. One reason may be that catastrophizing and self-efficacy at the initial assessment influences pain and functioning at longer-term outcomes (e.g., one year), but not at shorter-term outcomes such as at three months (Helminen et al., 2016). Supportive of this idea is work showing that self-efficacy (PSEQ at baseline) predicts the effects of long-term interventions, while no studies were found that show that self-efficacy predicts short-term intervention effects (Keefe et al., 2004; Arnstein et al., 1999).

The CART model and multiple logistic regression analysis showed that no potential predictor variables were found that identified participants with knee OA who experienced improved disability outcomes following education and exercise. This might simply be a reflection of the different factors that shape changes in pain and disability. Our data suggests some dissociation between improvements in pain and disability. Twenty two percent of participants met the criteria for both improved pain intensity and disability, whereas 14.6% patients improved only pain intensity, and 14.6% patients improved only disability, supporting the idea that different factors likely impact treatment success for these two variables. We also noted differences in which baseline variables characterized the different responders and non-responders for pain and for disability. Moreover, when comparing between pre and post intervention, the effect size (0.87) for pain intensity was larger than that (0.52) of disability, indicating that there are differences in the degree of effect between pain intensity and disability. Future studies might need to expand the range of variables measured to better understand factors that shape improvement in disability.

There is no data currently available to guide clinicians on what might be a relevant cut-off score on the FreKAQ to indicate clinically significant disruption of body perception. Our initial testing of the questionnaire showed that the mean score for healthy controls was 3.4 (Nishigami et al., 2017), so equivalent values in clinical populations should probably be ignored. Our present study provides some indication that a FreKAQ score of 17, which is close to 50% on the scale, might be an indicator that body perceptual disturbances are clinically relevant and may require specific attention in treatment planning. Further study is clearly required to address this issue.

There are some limits on the generalizability of our findings. First, our results are only valid for patients referred to physical therapy primarily for knee pain and may not apply to people who have not been formally referred or who have significant co-morbid pain conditions. Second, participants that dropped out of the study were significantly younger and reported lower pain intensity, PCS, OKS and FreKAQ scores than participants who were retained at follow-up. Unfortunately, we were unable to collect the reason for drop-out so it is unknown whether participants that dropped out had their symptoms improve, worsen, or remain the same. It is possible that higher dropout rates in younger participants might reflect the increased likelihood that they would still be working, making it more difficult for them to attend ongoing treatment sessions. Also, those with less severe symptoms may not have felt the need to continue to receive physical therapy. Therefore, this difference between participants that dropped out or were retained likely influences the CART analysis results, such that our findings are primarily generalizable to an older population and those with more severe symptoms. Despite this drop-out, at least in older participants with more severe symptoms, the clinical utility of the FreKAQ score and KL scale as predictors were evident.

A few limitations of the present study warrant consideration. First, participants in this study did not include a control group, this did not enable us to control for non-specific factors such as placebo response and regression to the mean so we cannot identify true treatment effect modifiers. However, given that this study's aims were hypothesis generating (versus developing a CPR), such interpretation of this data (i.e., as treatment effect modifiers) is unwarranted. Second, there are known limitations in the generalizability of CPRs in that devised models are often taken from homogenous samples and not often validated in subsequent samples (Stanton et al., 2016). However, given that our data came from orthopedic surgery departments in 14 different institutions, we believe that our model is based on a well-represented, diverse sample. Third, the present study did not include some parameters that may be important to clinical outcome post-exercise, such as evidence of central sensitization (Lluch E, et al., 2014), external knee adduction moment (Miyazaki et al., 2002; Astephen et al., 2008) or knee extensor strength (Hall et al., 2017). Because specialized instruments are needed to accurately quantify central sensitization, external knee adduction moment and, to a lesser extent, muscle strength, clinical measurement can be challenging. The potential predictive variables used in this study focus on assessments that can be conveniently undertaken in the clinic setting; adding assessment of knee extensor strength and central sensitization in future investigations may be fruitful. Fourth, habitual physical activity as a predictive parameter may be associated with response or non-response to exercise. Although we didn't measure habitual physical activity, an individual's activity capacity was taking into account by the physiotherapists to provide individually tailored and individually progressed exercise, which somewhat mitigates this issue.

5. Conclusions

Our results suggest that regardless of other variables, participants with knee OA who report low levels of body perception disruption (a FreKAQ score ≦ 17) and minimal structural changes (KL grade I) demonstrate significantly better outcomes from education and exercise therapy than other participants. Such findings suggest that people with low levels of disrupted body perception are likely to benefit from a simple education and exercise program. Conversely, education and exercise therapy alone might not be the most appropriate intervention for those with higher levels of disturbed self-perception and additional interventions that target this impairment might be needed to optimize outcome.

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Author contributions

S.T., T.N., and A.M. designed research; S.T., M.T., and T.Y. data collecting; S.T., and T.N. performed statistical analyses; S.T., T.N., B.M.W., T.R.S., A.M., M.T., T.Y., and T.U. interpreted results; S.T., T.N., B.M.W., A.M., M.T., T.Y., and T.U. wrote the paper, all authors discussed the results and commented on the manuscript.

Conflict of Interest

The authors declared no potential conflict of interests, with respect to the research, authorship, and/or publication of this article.

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Figure and Table Legends

Figure 1. Flow chart of participants through the study.

Figure 2. Factors to predict responders and non-responders

K-L = Kellgren and Lawrence

FreKAQ = The Fremantle Knee Awareness Questionnaire

Table 1. Standard exercise programme

Home program: 3days per week: Stretches as per group exercise sessions followed by 20 min of continuous walking and half squat, which going halfway down and holding the squat for five seconds two sets of twenty repetitions

Table 2 Baseline characteristics of participants and dropouts

* significant difference compared with dropouts ($p<0.05$).

† significant difference compared with non-responders ($p<0.05$).

Table 1 Standard exercise programme

Education	In Clinic Exercises	Home exercises
Etiology of knee Osteoarthritis	Stretches: quadriceps, hamstrings, gastrocnemius - 3 × 30 s hold each muscle group	Continuous walking - 20 mins x 3 days a week
Instruction on pain neurobiology		Stretches - as per clinic exercise 3 days a week
Information on the benefits of exercise	Non-weight –bearing concentric/eccentric quadriceps and hamstrings muscle strengthening - 2 × 20 repetitions for each muscle group	Non weight bearing strengthening exercises - as per clinic exercises 3 days a week
	Weight-bearing leg muscle strengthening: Squat - 2 × 20 repetitions	Weight bearing strengthening exercises - as per clinic exercises 3 days a week

Table 2 Characteristics of participants/dropouts and responders/non-responders

Factor	Baseline		Baseline (Pain)		Follow up (Pain)		Baseline (Disability)		Follow up (Disability)	
	Participants (n=150)	Dropouts (n=127)	Responders (n = 55)	Non-responders (n = 95)	Responders (n = 55)	Non-responders (n = 95)	Responders (n = 55)	Non-responders (n = 95)	Responders (n = 55)	Non-responders (n = 95)
Sex, Male/Female	27/123	31/96	13/42	14/81	-	-	10/45	17/78	-	-
Age (years)	71.1 ± 8.2*	67.3 ± 10.7	70.2±7.6	71.6±8.5	-	-	71.5±8.0	70.9±8.3	-	-
Body Mass Index (kg/m^2)	23.9 ± 3.1	23.7 ± 3.2	23.7±2.8	24.0±3.2	-		24.4±3.2	23.6±2.9	-	
Pain duration (weeks)	21.7 ± 65.5	19.0 ± 49.7	20.8±57.3	22.2±70.1	-	-	23.3±70.1	18.9±57.2	-	-
NSAIDs (Yes/No)	32/118	22/105	14/41	18/77	-	-	11/44	21/74	-	-
Intra-articular injections (Yes/No)	53/96	41/86	21/34	33/62	-	-	19/36	35/60	-	-
Knee effusion (Yes/No)	20/130	11/116	9/46	11/84	-	-	8/47	12/83	-	-
Disease severity (K-L grade)										

I	32	30	19†	13	-	-	13	19	-	-
II	53	60	21	32	-	-	17	36	-	-
III	43	27	12	31	-	-	16	27	-	-
IV	22	10	3	19	-	-	9	13	-	-
Pain Intensity Motion (NRS 0-10)	5.1 ± 1.8*	4.3 ± 2.4	4.9±2.0	5.1±1.6	1.5±0.9†	4.4±1.6	5.5±1.9†	4.8±1.6	2.6±1.8†	3.8±1.9
Range of Motion degrees (Extension)	-6.9 ± 7.2	-6.1 ± 7.2	-5.4±5.0†	-7.7±8.1	-2.8±3.9†	-6.0±6.2	-6.7±5.8	-7.0±7.9	-6.7±5.8	-7.0±7.9
Disability (OKS 0-48)	30.3 ± 7.7*	33.5 ± 9.5	32.0±7.5†	29.3±7.6	39.3±5.5†	31.5±7.9	27.4±7.8†	31.9±7.1	37.2±7.5†	32.8±7.9
Pain Catastrophising (PCS 0-52)	26.3 ± 9.9*	21.8 ± 12.0	24.7±10.0	27.2±9.7	15.8±10.0†	25.0±9.5	26.5±10.0	26.2±9.8	18.5±10.9†	23.4±10.1
Pain Self efficacy (PSEQ 0-60)	38.0 ± 11.9*	40.6 ± 12.9	40.7±12.7 †	36.3±11.1	46.3±11.1†	38.2±11.1	38.8±13.5	37.4±10.9	43.8±12.8†	39.7±10.9
Knee specific body perception	15.8 ± 7.9*	10.7 ± 7.2	12.4±7.5†	17.6±7.5	8.0±6.6†	15.5±7.4	14.8±7.3	16.2±8.2	10.0±7.6†	14.3±7.8

(FreKAQ 0-36)

* significant difference compared with dropouts ($p<0.05$).

† significant difference compared with non-responders ($p<0.05$).

Table 3 Multiple logistic regression analysis to predict pain intensity or disability

	Pain intensity			OKS		
Factor	OR	95%CI	P-value	OR	95%CI	P-value
Sex, Male/Female	0.914	0.341-2.449	0.858	0.765	0.288-2.029	0.590
Age (years)	1.014	0.964-1.068	0.586	0.983	0.937-1.031	0.481
Body Mass Index (kg/m^2)	1.069	0.936-1.220	0.324	0.925	0.820-1.043	0.202
Pain duration (weeks)	0.998	0.992-1.004	0.448	1.001	0.995-1.007	0.752
NSAIDs (Yes/No)	0.651	0.265-1.600	0.350	1.294	0.544-3.076	0.560
Pain intensity	0.902	0.495-1.644	0.736	0.594	0.334-1.057	0.077
Disease severity (K-L grade)	1.733	1.076-2.793	**0.024**	1.021	0.662-1.573	0.926
Range of Motion degrees (Extension)	0.994	0.932-1.060	0.844	0.986	0.932-1.043	0.622
Pain Catastrophising (PCS 0-52)	0.962	0.910-1.016	0.166	0.982	0.935-1.032	0.482
Pain Self efficacy (PSEQ 0-60)	0.968	0.928-1.009	0.127	0.991	0.955-1.027	0.605
Knee specific body perception (FreKAQ 0-36)	1.091	1.015-1.173	**0.018**	1.035	0.972-1.104	0.284

Figure 1 Flow chart of participants through the study.

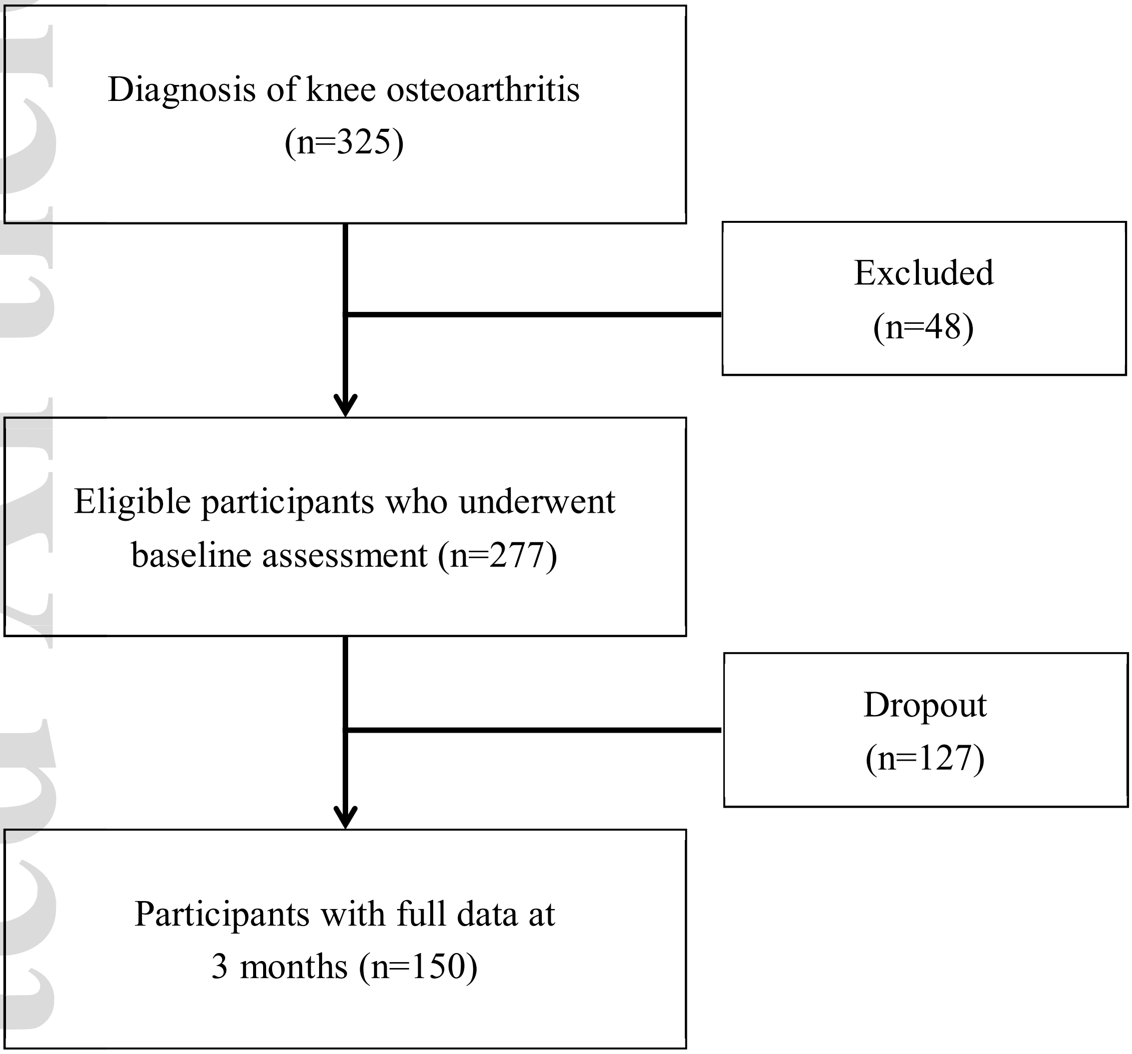
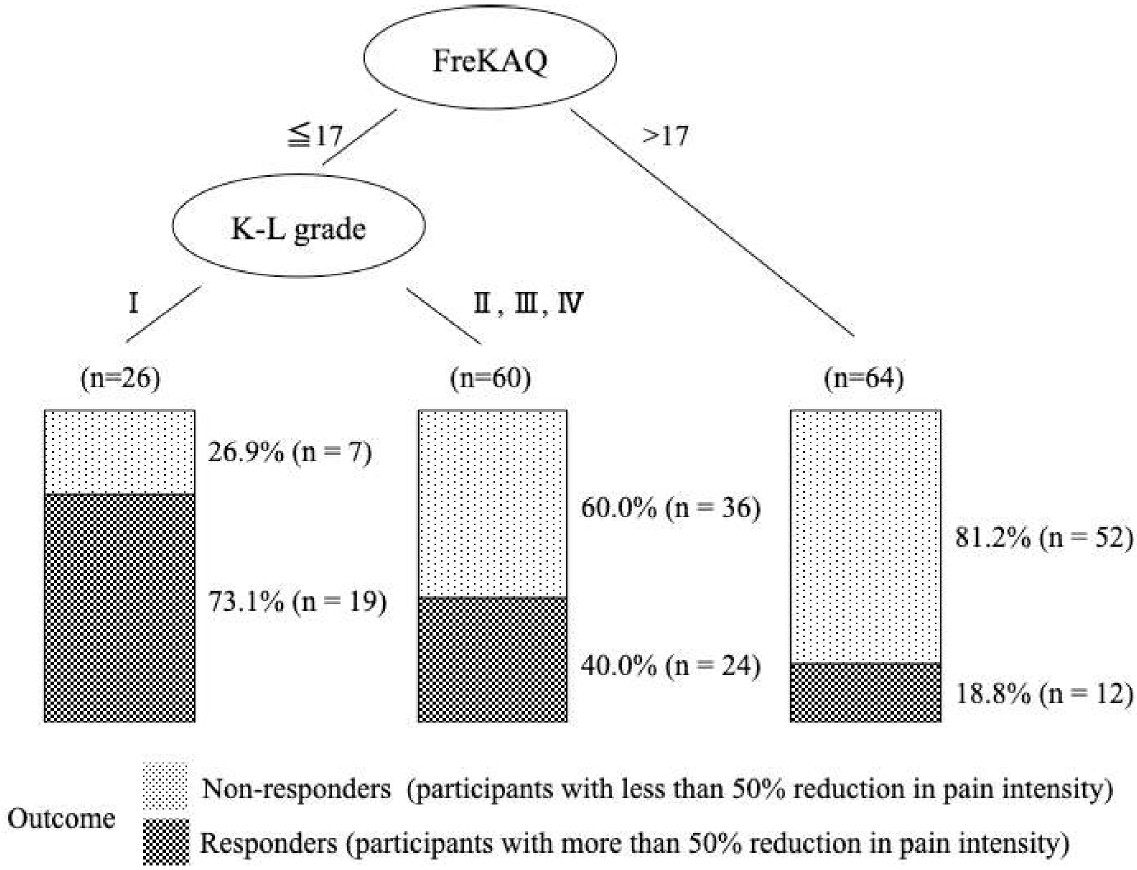


Figure 2 Factors to predict responders and non-responders



K-L = Kellgren and Lawrence

FreKAQ = The Fremantle Knee Awareness Questionnaire