Do psychosocial factors predict muscle strength, pain or physical performance in patients with knee osteoarthritis?

Isabel AC Baert[1, 2, 3], PhD, PT (isabel.baert@faber.kuleuven.be); Mira Meeus[2, 3, 4], PhD, PT (mira.meeus@uantwerpen.be); Armaghan Mahmoudian[1], MSc, PT (armahghan.mahmoudian@faber.kuleuven.be); Frank P Luyten[5], PhD, MD (frank.luyten@uzleuven.be); Jo Nijs[3,6], PhD, PT (jo.nijs@vub.ac.be) ; Sabine MP Verschueren[1], PhD, PT (sabine.verschueren@faber.kuleuven.be)

[1]Department of Rehabilitation Sciences, Faculty of Kinesiology and Rehabilitation Sciences, KULeuven, Belgium

[2]Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, University of Antwerp, Belgium

[3]Pain in Motion International Research Group, http://www.paininmotion.be

[4]Department of Rehabilitation Sciences and Physiotherapy, Ghent University, Ghent, Belgium

[5]Division of Rheumatology, UZ-KU Leuven, Belgium

[6]Departments of Physiotherapy, Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Belgium

Corresponding author

Dr. Isabel Baert - Department of Rehabilitation Sciences, KU Leuven

Tervuursevest 101, 3001 Heverlee , Belgium

Tel +32 478 97 13 60 Fax +32 16 32 91 92

Isabel.baert@faber.kuleuven.be

Short title for a running head: Do psychosocial factors predict clinical features in knee osteoarthritis?

This study was not financially supported by any study sponsor.

The authors declare that they have no conflicts of interest.

ABSTRACT

Objective. To examine the relationship of psychosocial factors, namely pain catastrophizing, kinesiophobia and maladaptive coping strategies, with muscle strength, pain and physical performance in patients with knee osteoarthritis (OA) related symptoms.

Methods. A total of 109 women (64 with knee OA related symptoms) with a mean age of 65.4 (49 to 81) were recruited for this study. Psychosocial factors were quantified by the Pain Catastrophizing Scale, Tampa Scale for Kinesiophobia, and Pain Coping Inventory. Clinical features were assessed using isometric and isokinetic knee muscle strength measurements, Visual Analogue Scale, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and functional tests. Associations were examined using correlation and regression analysis.

Results. In knee OA patients, pain catastrophizing, kinesiophobia and coping strategy explained a significant proportion of the variability in isometric knee extension and flexion strength (6.3%-9.2%), accounting for more overall variability than some demographic and medical status variables combined. Psychosocial factors were not significant independent predictors of isokinetic strength, knee pain or physical performance.

Conclusions. In understanding clinical features related to knee OA such as muscle weakness, pain catastrophizing, kinesiophobia and coping strategy, might offer something additional beyond what might be explained by traditional factors, underscoring the importance of a biopsychosocial approach in knee OA management. Further research on individual patient characteristics that mediate the effects of psychosocial factors is however required in order to create opportunities for more targeted, personalized treatment for knee OA.

Keywords: Knee osteoarthritis - Psychosocial factors - Muscle strength - Pain - Function

INTRODUCTION

Knee osteoarthritis (OA) is the most common chronic joint disease in elderly, with a higher prevalence among women (1, 2). Given the increase in life expectancy, the number of people living with severe knee OA is expected to grow and we need to improve our understanding of the disease and related factors to create opportunities for more targeted treatment options.

In primary care, pain is the key symptom for knee OA patients to seek medical treatment. More pain is often associated with difficulties performing daily activities, such as walking short or long distances, sit-to-stand activities and stair climbing, all of which can lead to limitations participating in social and outdoor activities and reduction in quality of life (3, 4). Knee OA patients also often demonstrate muscle weakness in lower extremity muscles, particularly in the quadriceps (5, 6), and this muscle weakness seems to be related to more pain and reduced function (7). Causes of muscle weakness in knee OA are likely to be multifactorial and pain is commonly presumed to be a major source of inhibition in the ability to voluntarily activate muscles around the knee joint (7). So, bi-directional relationships seem to exist between pain and muscle strength, whereby pain can influence muscle strength, and in turn be influenced by these factors (8), leading to a downward cascade in physical performance.

Over the past decades our understanding of chronic disease processes has increased substantially and it is now well established that the biomedical model falls short in explaining and treating chronic musculoskeletal pain conditions, such as OA (9). Traditionally, OA-related pain has been considered a nociceptive pain, directly associated to the degree of structural joint damage. However, studies showed inconsistent results investigating associations between structural joint abnormalities, measured by radiography or Magnetic Resonance Imaging, and clinical features of the disease (10, 11). OA pain experience and related dysfunctions seem to be multidimensional in nature, making a broader biopsychosocial approach to knee OA management indispensable.

Research suggests that psychosocial variables, including pain catastrophizing, kinesiophobia and maladaptive pain coping styles, may be important in explaining variations in pain and physical performance in knee OA patients (12-16). Pain catastrophizing refers to the tendency to focus on and magnify pain sensations and to feel helpless in the face of pain (17) and kinesiophobia is defined as excessive, irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury (18). Pain coping can be described as the behavioral and cognitive attempts to tolerate or to deal with pain (19). Active pain coping strategies have been defined as individuals' attempts to manage their pain through their own resources. In contrast, pain responses such as resting, negative thoughts, avoidance behavior, and guarding the painful body part have

been labeled as passive coping (20). OA patients who catastrophize about pain, who have pain-related fear or who use a maladaptive coping style report more pain and higher levels of physical disability (12-16). However, it is currently unknown whether psychosocial variables explain variations in objective measures of muscle strength in people with OA.

Understanding the relative importance of psychosocial variables in the clinical expression of the disease is important as psychosocial factors may act as therapy effect modifiers (characteristics that predict treatment effects) (21), or outcome predictors (characteristics that predict outcome independent of therapy) (22), both useful for clinicians to select the best treatment for an individual patient or to provide patient-specific information on prognosis.

The primary aim of this study was to examine the relationship between psychosocial factors, i.e. the degree of pain catastrophizing, kinesiophobia and maladaptive pain coping style, and muscle strength in patients with knee OA related symptoms. Secondly, the relationship between psychosocial factors and pain and physical performance was investigated. Our main hypothesis is that these psychosocial factors are related to clinical OA features, i.e. that higher degrees of pain catastrophizing and kinesiophobia and maladaptive pain coping styles are related to less muscle strength, higher pain levels and poorer physical functioning.

MATERIALS AND METHODS

Participants

One hundred and nine women were selected for this study (Figure 1). All procedures were approved by the local ethical committee of Biomedical Sciences KU Leuven. A written informed consent was obtained from each participant. The study was conducted in accordance with the declaration of Helsinki.

Women with knee OA related symptoms were recruited by a rheumatologist or orthopedic surgeon during routine consultations at the University Hospitals Leuven. Asymptomatic women were recruited through several regional cultural and social organizations. Overall, subjects were excluded if they had musculoskeletal disorders other than knee OA in one or both limbs in the last six months, previous surgery of lower extremities or low back, neurological disorders or chronic intake of corticoids or contra-indications for Magnetic Resonance Imaging (MRI).

All participants were referred for a physical exam and standard anterior-posterior weight-bearing radiographs in fixed knee flexion (Siemens, Siregraph CF, Agfa CR HD5.0 detector 24*30) were taken bilaterally. Radiographic readings were done by a single experienced reader (FPL) and each tibiofemoral compartment was graded using the Kellgren and Lawrence (K&L) scale with recent adjustment (23). For subjects with knee OA symptoms and a K&L grade of 0,1 or 2^-, an additional MRI of the knee was performed on a 3.0 T scanner (Philips Achieva TX, Philips Medical Systems, Best, The Netherlands) using an eight-channel phased array knee coil in a non-weight-bearing supine position. Semiquantitative scoring of specific structural features in the tibiofemoral joint was performed separately by two readers (NN and GVDS) using the standardized Boston-Leeds Osteoarthritis Knee Score (BLOKS) scoring system (24) (data not shown). Full agreement was achieved for 91% of all scored items. Disagreements were resolved by consensus.

In women with knee OA related symptoms and presence of minimum grade 2^+ (osteophytes and joint space narrowing in the same compartment) on K&L scale on radiography, the American College of Rheumatology (ACR) classification criteria (25) were verified, including knee pain, stiffness less than 30 minutes and crepitus, These patients were classified as having **established knee OA**, indicating moderate to severe disease severity. The tibiofemoral compartment with presence of minimum grade 2^+ on K&L scale on radiography was indicated as the involved compartment. As strict radiographic criteria do not suffice to capture early joint degeneration, MRI based classification criteria were used to define patients with **early knee OA** (26). Subjects with early knee OA showed a combination of knee pain, a K&L grade 0, 1 or 2^-(osteophytes only) on radiography and presence of at least two of four specific MRI criteria described by Luyten et al. (26): (I) ≥ BLOKS grade 2 for size cartilage loss, (II) ≥ BLOKS grade 2 for percentage full-thickness cartilage loss , (III) signs of meniscal degeneration and (IV) ≥ BLOKS grade 2 for size of bone marrow lesions (BMLs) in any one compartment. The tibiofemoral compartment that met these MRI criteria was indicated as the involved compartment.

Patients with signs of OA in the patellofemoral joint on radiography or MRI were excluded.

In order to compare the characteristics of the symptomatic knee OA group to a non-diseased group, 45 **control subjects** were also included in the study. They were asymptomatic with no history of knee OA. On radiography both knees had a K&L grade 0 or 1.

The (most) affected side ((most) symptomatic with (highest) structural severity) for the symptomatic knee OA subjects and an at random side for controls was selected for further analysis.

Independent variables - Assessment of psychosocial factors

Pain Catastrophizing

The Dutch Pain Catastrophizing Scale (PCS) is a self-reported questionnaire aiming at assessing the degree to which the participant engages in pain catastrophizing, consisting of 13 items describing different thoughts and feelings persons may experience when they have pain. Each item is rated using a 5-point Likert scale, from 0 (not at all) to 4 (all the time). A total score is counted by summing all individual item scores (range 0-52). Higher scores correspond to more severe catastrophic thoughts about pain. The PCS has acceptable psychometric properties (27).

Kinesiophobia

The Tampa Scale for Kinesiophobia (TSK) is a 17-item questionnaire that assesses fear of (re)injury due to movement. Items are scored on a 4-point Likert scale and total score is calculated (1-4 for each item), after inversion of the scores of items 4, 8, 12 and 16. Total scores range from 17 to 68, with scores ≤ 37 suggesting low fear of movement and scores > 37 indicating high fear of movement. The Dutch TSK is a reliable and valid measure (28).

Pain Coping Style

The Pain Coping Inventory (PCI) consists of 6 scales (33 items) measuring cognitive and behavioral pain-coping strategies representing two pain coping dimensions: active (subscales distraction, transformation, and reducing demands) and passive (subscales resting, retreating, and worrying). Patients are asked to indicate how often they apply a certain strategy when dealing with pain on a 4-point Likert scale ranging from 1 (hardly ever) to 4 (very often). A total score was calculated for each coping dimension and transformed into a percentage. Psychometric properties are reported as good in different patient populations (20).

Dependent variables – Assessment of muscle strength, pain and physical performance

Muscle strength

Maximal voluntary knee muscle strength was measured using the Biodex System 3 Pro (Biodex Medical System, Shirley, NY, USA). Before every test session, the Biodex was calibrated and measurements were performed according to standard procedures.

Muscle strength was measured isometrically (static) for extension and flexion, both in a 60° and 90° flexion position and isokinetically (dynamic) for extension at low speed (60°/second) and high speed (240°/second) in order to examine different aspects of muscle strength. Each isometric test was performed three times with maximal

contraction for five seconds and ten seconds rest between trials. For isokinetic testing, three trials were performed for extension at 60°/second and five trials for extension at 240°/second.

All subjects received the same instructions and encouragements to achieve maximal effort. For each test the peak torque normalized for body weight (Nm/kg) of all trials was used.

Intra-rater reliability was assessed by repeated testing on a subset of 12 subjects. High to very high intraclass correlation coefficients were found for all strength measurements between test and retest (ICC between 0.75 and 0.98).

Pain and physical performance

The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Dutch version) has been developed for use among knee and/or hip OA patients and is shown to be valid and reliable (29). It consists of 24 items rated on a 5-point Likert scale divided into 3 subscales (i.e. pain, stiffness and physical function). To assess subjects' pain and subjective physical performance, WOMAC subscales "pain" and "physical function", respectively, were used. For each subscale, a transformed score from 0 to 100 was calculated, with 100 as best possible result.

In addition, pain intensity was measured with the Visual Analogue Scale (VAS), consisting of a 100-mm line on which the subject places a mark between the left side (0), representing "no pain", and the right side (100), representing "worst pain imaginable". The VAS is found to be a reliable measure of pain (30).

Objective physical performance was assessed by two functional tests. The Timed "Up & Go" test (TUG) measured the time taken to stand from a chair, walk three meters, turn around, return to the chair and sit down. The "Stair Climbing Test (SCT)" measured the time required to ascend five steps, turn around and descend five steps. These tests were performed three times and a mean value was calculated. Both tests have good reliability and validity (31, 32).

Data analysis

Analyses were performed with SPSS for Windows, version 23.0 with an α level of 0.05.

Descriptive statistics were carried out to summarize study population characteristics. Normality of data was evaluated using the Shapiro-Wilk test. Although small deviations from normality were observed for some measures, the large number of observations (N=64 and N=45) allowed valid parametric testing.

Correlation and regression analyses were performed in the group with knee OA related symptoms (N=64).
First, correlation analyses were performed to examine the associations between psychosocial factors and clinical features related to knee OA. Results of the correlation analyses were expressed as Pearson correlation coefficients (r) and P-values.

Multivariable linear regression models were fitted to assess the unique contribution of *psychosocial factors* (independent variables: pain catastrophizing, kinesiophobia and pain coping style) to the *clinical features related to knee OA* (dependent variables: pain, physical performance and muscle strength). The assumptions of the linear regression models were checked by analysis of the residuals (normality, homoscedasticity, linear relationship).
Associations between psychosocial factors and muscle strength (normalized for body weight) were determined accounting for age, pain and structural severity. The association between psychosocial factors and pain (VAS and WOMAC pain) was determined accounting for structural severity, whereas the association between psychosocial factors and subjective and objective physical performance (WOMAC function, TUG and SCT) was determined accounting for age, pain, BMI and structural severity. Results of regression analyses were expressed as standardized regression coefficients (β) , P-values and coefficients of partial determination (partial R^2).

RESULTS

Details of subject characteristics are presented in Table 1. Subjects with knee OA related symptoms were comparable to asymptomatic subjects with respect to age and height, but had significantly higher weight (P=0.004) and higher BMI (P=0.003). As expected, knee OA subjects had significantly more pain (all P<0.001), more physical disability (all $P\leq$0.003) and less muscle strength (all P<0.001) compared to asymptomatic subjects.
No significant differences were found between groups for the degree of pain catastrophizing. Compared to the asymptomatic group, patients with knee OA related symptoms showed significantly more kinesiophobia (P=0.013) and used significantly more active (P=0,024) and passive coping (P=0.027).

Correlation analyses (Table 2) revealed that the degree of pain catastrophizing was significantly and negatively correlated with isometric knee flexion strength (r=-0.259; P=0,039 and r=-0,309; P=0,013). The degree of kinesiophobia was significantly and negatively correlated with isometric knee extension strength (r=-0.261; P=0.037). Although statistically significant, the correlation coefficients found in this study were all rather low, indicating weak correlations.

Multivariable linear regression: association between psychosocial factors and clinical features related to knee OA

Association with muscle weakness (Table 3 and 4)

In this study population, the degree of **pain catastrophizing** was significantly associated with isometric extension strength (in 60°: β=-0.262; P=0.041; Partial R^2=0,067) and isometric flexion strength (in 60°: β=-0.259; P=0.040; Partial R^2=0,065 – in 90°: β=-0.308; P=0.013; Partial R^2=0,092). More pain catastrophizing was associated with less isometric knee extension and flexion strength. Age, pain and structural severity accounted for 3,2%-7,5% of the variability in isometric knee strength and pain catastrophizing accounted for an additional 6.5%-9.2% of the variability.

The degree of **kinesiophobia** and the use of an **active coping style** were significantly associated with isometric extension strength (β=-0.255; P=0.045; Partial R^2=0,063 and β=0.255; P=0.047; Partial R^2=0,063, respectively). More kinesiophobia and less use of an active coping style were associated with less isometric knee extension strength. Age, pain and structural severity accounted for 3,2%-5,4% of the variability in isometric knee extension strength and kinesiophobia and the use of an active coping style each accounted for an additional 6,3% of this variability.

Passive coping was not significantly associated with isometric knee muscle strength.

None of the psychosocial factors were significantly associated with isokinetic muscle strength. Pain was significantly associated with isokinetic knee extension strength at high speed (240°/sec) (β=0.255; P=0.034; Partial R^2=0,073) and accounted for 7,3% of the variability in isokinetic knee extension strength. In general, age, pain and structural severity accounted for 7.3%-8.1% of the variability in isokinetic knee strength and psychosocial factors were not significant independent predictors of isokinetic extension strength.

Association with knee pain and physical performance (Table 5)

In knee OA patients, none of the psychosocial factors showed a significant association with knee pain (measured by VAS and WOMAC pain) and physical performance (measured by WOMAC function, TUG and SCT). In this study, psychosocial factors accounted for less than 3.8% of the variability in knee pain and physical performance.

DISCUSSION

This study examined the relationship between psychosocial factors, i.e. pain catastrophizing, kinesiophobia and maladaptive pain coping style, and muscle strength, knee pain and physical performance in patients with knee OA related symptoms. Results indicate that none of the studied psychosocial factors are independently associated with

knee pain or physical performance. Pain catastrophizing, kinesiophobia and coping strategy did explain a small, but statistically significant proportion of the variance in isometric knee extension and flexion strength (6.5%-9.2%, 6.3% and 6.3%, respectively). These results were obtained after verifying some general variables (age, pain, BMI and structural severity) as they are believed to be important in explaining muscle strength in OA patients. Psychosocial variables accounted for more overall variance in isometric muscle strength than demographic and medical status variables combined.

Association with knee pain and physical performance

In previous studies, pain catastrophizing, kinesiophobia and maladaptive coping style have been associated with knee pain and physical performance in knee OA patients (12-15). In addition, in patients undergoing total knee replacement, high pre-surgical levels of pain catastrophizing and maladaptive pain coping strategies predicted post-surgical pain, but fear of movement did not contribute to knee function (33). Evidence for the role of catastrophizing, kinesiophobia, and inadequate coping strategies in maintaining chronic pain and related disability has also been provided in patients with fibromyalgia, chronic low back pain, and other chronic pain disorders (34-36). In chronic low back pain for instance, it has been shown that a decrease in catastrophizing mediated improvements in physical performance, even when there was no opportunity to be physical active (34). In patients with chronic pain and chronic fatigue syndrome, a clear association between pain catastrophizing and physiological exercise capacity performance was shown (37). In contrast to these findings, our study could not reveal an independent association between these psychosocial factors on one hand and knee pain or subjective and objective physical performance on the other hand.

When trying to determine reasons for the differences between our and previous findings, it is important to realize that in knee OA, the pain experience is likely to be influenced by a multitude of structural, physical, and psychosocial factors (38), which are different for every individual patient. Over the past decades, there is growing body of research suggesting that altered central nociceptive processing mechanisms play a significant role in a subgroup of knee OA patients (around 30%), particularly those with moderate to severe symptomatic OA (39, 40). In this subgroup, the clinical picture is dominated by sensitization of the central nervous system and enhanced nociceptive facilitation due to psychosocial factors, rather than by biomechanical or structural factors causing nociceptive pain (39, 41, 42). In contrast, in patients with predominantly nociceptive pain the clinical picture is dominated by biomechanical or structural factors. This implies that in knee OA different people experience pain for different reasons. In our study and in previous studies, no specific methods to diagnose potential involvement

of central sensitization (i.e. quantitative sensory testing, brain imaging techniques, efficacy of centrally acting drugs) were used, therefore it is unknown which pain phenotypes are present in the different study populations. Dominance of central sensitization is more likely to be present in patients with moderate to severe symptomatic OA (40). Although our knee OA patients were all symptomatic (mean WOMAC pain=72.7, mean VAS=35), only 25% had a K&L grade ≥ 3.

Within this context, it is not surprising that significant associations between psychological factors on one hand and pain or physical performance on the other hand were not discovered in our patient population, emphasizing possible dependence on specific study population characteristics. Differences in the characteristics of the study populations in terms of pain phenotypes between studies might explain the discrepancies in the results. Psychosocial factors might predict pain and physical performance in some patients rather than in the whole knee OA population.

Association with muscle strength

The muscles around the knee have an important function as they produce movement but also absorb limb loading and provide dynamic joint stability. Quadriceps muscle weakness is well documented among knee OA patients (5, 6) and evidence supports the use of strengthening exercises to improve pain and physical function in this population (43).

Our study findings indicate that knee pain is a significant predictor of isokinetic knee extension strength at high speed (240°/sec), explaining 7.3% of the variability in muscle strength. This finding suits our current understanding of nociception-motor interaction in patients with (chronic) pain (44). The interaction between nociception and motor output is very complex, especially in cases of chronic nociception such as in OA. Current knowledge of nociception-motor interactions (44) has informed us that nociceptive stimuli result in cortical delay of motor output in humans and reduced activity of the painful muscle. People show adapted movement patterns when they are in pain. Nociception impairs motor output through central mechanisms: activated neurons in the somatosensory-cortex produce a pain-dependent inhibitory input to the primary motor cortex (both ipsilateral and contralateral), and tonic human muscle nociception results in long-lasting inhibition of the primary motor cortex (45). This way, nociception may indeed prevent maximal voluntary knee muscle strength, explaining our observations. In our study, knee pain was not significantly associated with isometric muscle strength or isokinetic muscle strength at

low speed. These muscle strength measures are less challenging than isokinetic muscle strength at high speed, which might explain the lack of significant associations.

The degree of pain catastrophizing, kinesiophobia and the use of active coping independently predict isometric knee extension and flexion strength. The psychosocial variables accounted for more overall variability in isometric muscle strength than demographic and medical status variables (age, pain, BMI and structural severity) combined. These findings fit in the cognitive behavioural model of fear of movement (36), which is based on the assumption that, for some patients, pain experience will lead to fear of movement or to a maladaptive coping style (avoidance behaviour). In the long term, avoidance of movement and physical activity might result in physical changes (e.g. muscle weakness) and psychological changes (e.g. depression, more fear of movement) that contribute to the symptom complex of chronic pain patients (36).

Our results suggest that, in understanding clinical features related to knee OA such as decrease in muscle strength, pain catastrophizing, kinesiophobia and coping strategy, offer something additional beyond what might be explained by traditional factors. In accordance with the biopsychosocial approach in chronic pain management, physical as well as psychosocial impairments could be addressed in knee OA management, with individual treatment considerations for each patient. In most knee OA patients, local application of different modalities with attention to biological features is appropriate. Indeed, exercise therapy and manual therapy for example are strongly recommended in most of the current evidence-based guidelines for OA management (43). However, interventions focused on decreasing pain catastrophizing and kinesiophobia and improve self-management might also be useful and are currently only sparsely used. Such interventions include, but are not limited to, therapeutic pain neuroscience education, graded exposure, graded activity, and pain coping skills training. Studies have shown positive results for integrated exercise and psychological treatments in a variety of chronic conditions including cancer (46), low back pain (47) and fibromyalgia (48). In knee OA, a combined treatment comprising of pain coping skills training and exercise therapy improved patient outcome (49).

The present study has some limitations. First, investigating associations between psychosocial factors and clinical features, we accounted for age, pain, BMI and structural severity. However, other factors, such as work, habitual physical activity, symptom duration or current treatment, that were not taken into account, could also have influenced clinical features. It is also important to note that no correction for multiple testing was used in this study. Furthermore, the study population included only women as knee OA is more common among women and gender-specific characteristics are avoided, with consequently a more homogeneous study population which

improved statistics. However, therefore, we need to be careful in generalizing the study results to the male OA population. Additionally, it has to be mentioned that in our knee OA subjects, the level of pain catastrophizing was not significantly different from asymptomatic subjects and was rather low (mean 16.0 (SD 9.7)), as it is indicated that a total PCS score of 30 or more represents a clinically relevant level of catastrophizing (50), which could have influenced the results. Lastly, the group size was rather small in this study which precludes definitive conclusions at this stage.

To improve our understanding of OA-related factors and to create opportunities for more targeted treatment, further research is necessary to integrate our current understanding of (OA) pain, including the involvement of central sensitization and nociception-motor interactions**.** Future studies with a larger sample size, using analyses that account for all variables that might be important in explaining clinical features related to knee OA, should re-explore the associations studied here within each of the different pain phenotypes-based subgroups in the OA population.

In addition, as the effect of psychosocial factors on physical performance might be mediated through pain and muscle strength, these mediating factors merit investigation in future studies. A randomized controlled trial could be performed in which these mediating factors are manipulated in order to investigate the association between psychosocial factors (cause) and physical performance (consequence).

In conclusion, results of this study suggest that psychosocial factors, namely pain catastrophizing, kinesiophobia and coping style, might play a significant role in dysfunctions such as muscle weakness in knee OA patients, underscoring the role of a biopsychosocial approach in knee OA management. However, further research on individual patient characteristics that mediate the effects of psychosocial factors is required in order to create opportunities for more targeted, personalized treatment for knee OA.

ACKNOWLEDGEMENTS

We would like to thank S. Verweijen and C. Smolders for their assistance in performing the clinical measurements and W. Van Hoef for the radiographic assessment, S. Ghysels for performing the MRI scans and N. Noppe and G. Vanderschueren for scoring the MRI scans with the BLOKS scoring system.

This study was not financially supported by any study sponsor.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Ma VY, Chan L, Carruthers KJ. The Incidence, Prevalence, Costs and Impact on Disability of Common Conditions Requiring Rehabilitation in the US: Stroke, Spinal Cord Injury, Traumatic Brain Injury, Multiple Sclerosis, Osteoarthritis, Rheumatoid Arthritis, Limb Loss, and Back Pain. Arch Phys Med Rehabil. 2014;95:986-95.

2. Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2010;18(1):24-33.

3. Davis MA, Ettinger WH, Neuhaus JM, et al. Knee osteoarthritis and physical functioning: evidence from the NHANES I Epidemiologic Followup Study. J Rheumatol. 1991;18(4):591-8.

4. Collins JE, Katz JN, Dervan EE, et al. Trajectories and risk profiles of pain in persons with radiographic, symptomatic knee osteoarthritis: data from the osteoarthritis initiative. Osteoarthritis Cartilage. 2014;22(5):622-30.

5. Lewek MD, Rudolph KS, Snyder-Mackler L. Quadriceps femoris muscle weakness and activation failure in patients with symptomatic knee osteoarthritis. J Orthop Res. 2004;22(1):110-5.

6. Palmieri-Smith RM, Thomas AC, Karvonen-Gutierrez C, et al. Isometric quadriceps strength in women with mild, moderate, and severe knee osteoarthritis. Am J Phys Med Rehabil. 2010;89(7):541-8.

7. Bennell KL, Wrigley TV, Hunt MA, et al. Update on the role of muscle in the genesis and management of knee osteoarthritis. Rheum Dis Clin North Am. 2013;39(1):145-76.

8. Sale JE, Gignac M, Hawker G. The relationship between disease symptoms, life events, coping and treatment, and depression among older adults with osteoarthritis. J Rheumatol. 2008;35(2):335-42.

9. Nijs J, Roussel N, Paul van Wilgen C, et al. Thinking beyond muscles and joints: therapists' and patients' attitudes and beliefs regarding chronic musculoskeletal pain are key to applying effective treatment. Man Ther. 2013;18(2):96-102.

10. Baert IA, Staes F, Truijen S, et al. Weak associations between structural changes on MRI and symptoms, function and muscle strength in relation to knee osteoarthritis. Knee Surg Sports Traumatol Arthrosc. 2014;22:2013-25.

11. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: a systematic search and summary of the literature. BMC Musculoskelet Disord. 2008;9:116.

12. Steultjens MP, Dekker J, Bijlsma JW. Coping, pain, and disability in osteoarthritis: a longitudinal study. J Rheumatol. 2001;28(5):1068-72.

13. Somers TJ, Keefe FJ, Pells JJ, et al. Pain catastrophizing and pain-related fear in osteoarthritis patients: relationships to pain and disability. J Pain Symptom Manage. 2009;37(5):863-72.

14. Keefe FJ, Lefebvre JC, Egert JR, et al. The relationship of gender to pain, pain behavior, and disability in osteoarthritis patients: the role of catastrophizing. Pain. 2000;87(3):325-34.

15. Heuts PH, Vlaeyen JW, Roelofs J, et al. Pain-related fear and daily functioning in patients with osteoarthritis. Pain. 2004;110(1-2):228-35.

16. Urquhart DM, Phyomaung PP, Dubowitz J, et al. Are cognitive and behavioural factors associated with knee pain? A systematic review. Semin Arthritis Rheum. 2015;44(4):445-55.

17. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. Clin J Pain. 2001;17(1):52-64.

18. Kori SH, Miller RP, Todd DD. Kinesiophobia: a new view of chronic pain behavior. Pain management. 1990;35-43

19. Kraaimaat FW, Bakker A, Evers AWM. Pijncoping-strategieën bij chronische pijnpatiënten: de ontwikkeling ontwikkeling van de Pijn Coping Inventarisatielijst (PCI). Gedragstherapie 1997;30:185-201

20. Kraaimaat FW, Evers AW. Pain-coping strategies in chronic pain patients: psychometric characteristics of the pain-coping inventory (PCI). Int J Behav Med. 2003;10(4):343-63.

21. Kraemer HC, Wilson GT, Fairburn CG, et al. Mediators and moderators of treatment effects in randomized clinical trials. Arch Gen Psychiatry. 2002;59(10):877-83.

22. Smeets RJ, Maher CG, Nicholas MK, et al. Do psychological characteristics predict response to exercise and advice for subacute low back pain? Arthritis Rheum. 2009;61(9):1202-9.

23. Felson DT, Niu J, Guermazi A, et al. Defining radiographic incidence and progression of knee osteoarthritis: suggested modifications of the Kellgren and Lawrence scale. Ann Rheum Dis. 2011;70(11):1884-6.

24. Hunter DJ, Lo GH, Gale D, et al. The reliability of a new scoring system for knee osteoarthritis MRI and the validity of bone marrow lesion assessment: BLOKS (Boston Leeds Osteoarthritis Knee Score). Ann Rheum Dis. 2008;67(2):206-11.

25. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum. 1986;29(8):1039-49.

26. Luyten FP, Denti M, Filardo G, et al. Definition and classification of early osteoarthritis of the knee. Knee Surg Sports Traumatol Arthrosc. 2012;20(3):401-6.

27. Van Damme S, Crombez G, Bijttebier P, et al. A confirmatory factor analysis of the Pain Catastrophizing Scale: invariant factor structure across clinical and non-clinical populations. Pain. 2002;96(3):319-24.

28. Goubert L, Crombez G, Van Damme S, et al. Confirmatory factor analysis of the Tampa Scale for Kinesiophobia: invariant two-factor model across low back pain patients and fibromyalgia patients. Clin J Pain. 2004;20(2):103-10.

29. Roorda LD, Jones CA, Waltz M, et al. Satisfactory cross cultural equivalence of the Dutch WOMAC in patients with hip osteoarthritis waiting for arthroplasty. Ann Rheum Dis. 2004;63(1):36-42.

30. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med. 2001;8(12):1153-7.

31. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. 1991;39(2):142-8.

32. Rejeski WJ, Ettinger WH, Jr., Martin K, et al. Treating disability in knee osteoarthritis with exercise therapy: a central role for self-efficacy and pain. Arthritis Care Res. 1998;11(2):94-101.

33. Baert IA, Lluch E, Mulder T, et al. Does pre-surgical central modulation of pain influence outcome after total knee replacement? A systematic review. Osteoarthritis Cartilage. 2016;24(2):213-23.

34. Moseley GL. Evidence for a direct relationship between cognitive and physical change during an education intervention in people with chronic low back pain. Eur J Pain. 2004;8(1):39-45.

35. Hassett AL, Cone JD, Patella SJ, et al. The role of catastrophizing in the pain and depression of women with fibromyalgia syndrome. Arthritis Rheum. 2000;43(11):2493-500.

36. Vlaeyen JW, Linton SJ. Fear-avoidance and its consequences in chronic musculoskeletal pain: a state of the art. Pain. 2000;85(3):317-32.

37. Nijs J, Van de Putte K, Louckx F, et al. Exercise performance and chronic pain in chronic fatigue syndrome: the role of pain catastrophizing. Pain Med. 2008;9(8):1164-72.

38. Sharma L, Cahue S, Song J, et al. Physical functioning over three years in knee osteoarthritis: role of psychosocial, local mechanical, and neuromuscular factors. Arthritis Rheum. 2003;48(12):3359-70.

39. Lluch Girbes E, Nijs J, Torres-Cueco R, et al. Pain treatment for patients with osteoarthritis and central sensitization. Phys Ther. 2013;93(6):842-51.

40. King CD, Sibille KT, Goodin BR, et al. Experimental pain sensitivity differs as a function of clinical pain severity in symptomatic knee osteoarthritis. Osteoarthritis Cartilage. 2013;21(9):1243-52.

41. Lluch E, Torres R, Nijs J, et al. Evidence for central sensitization in patients with osteoarthritis pain: a systematic literature review. Eur J Pain. 2014;18(10):1367-75.

42. Fingleton C, Smart K, Moloney N, et al. Pain sensitization in people with knee osteoarthritis: a systematic review and meta-analysis. Osteoarthritis Cartilage. 2015;23(7):1043-56.

43. Larmer PJ, Reay ND, Aubert ER, et al. A systematic review of guidelines for the physical management of osteoarthritis. Arch Phys Med Rehabil. 2013.

44. Nijs J, Daenen L, Cras P, et al. Nociception Affects Motor Output A Review on Sensory-motor Interaction With Focus on Clinical Implications. Clinical Journal of Pain. 2012;28(2):175-81.

45. Le Pera D G-NT, Valeriani M, Oliviero A, Di Lazzaro V, Tonali PA, Arendt-Nielsen L. . Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. Clin Neurophysiol. 2001;112:1633-41.

46. May AM, Van Weert E, Korstjens I, et al. Improved physical fitness of cancer survivors: a randomised controlled trial comparing physical training with physical and cognitive-behavioural training. Acta Oncol. 2008;47(5):825-34.

47. Smeets RJ, Vlaeyen JW, Kester AD, et al. Reduction of pain catastrophizing mediates the outcome of both physical and cognitive-behavioral treatment in chronic low back pain. J Pain. 2006;7(4):261-71.

48. van Koulil S, van Lankveld W, Kraaimaat FW, et al. Tailored cognitive-behavioral therapy and exercise training for high-risk patients with fibromyalgia. Arthritis Care Res (Hoboken). 2010;62(10):1377-85.

49. Bennell KL, Ahamed Y, Jull G, et al. Physical therapist-delivered pain coping skills training and exercise for knee osteoarthritis: Randomized controlled trial. Arthritis Care Res (Hoboken). 2015.

50. Sullivan MJL, Bishop S, Pivik J. The Pain Catastrophizing Scale: Development and validation. Psychol Assess. 1995;7:524-32

Table 1. Characteristics of patients with knee OA related symptoms and control subjects*

Characteristics	Symptomatic Knee OA subjects *n* = 64	Asymptomatic subjects *n* = 45	*P*
Age, years	65.6 (7.3)	65.0 (5.2)	0.628
Weight, kg	72.3 (10.8)	66.5 (9,6)	0.004†
Height, m	1.62 (0.06)	1.62 (0.05)	0.946
BMI, kg/m^2	27.8 (4.4)	25.4 (3.4)	0.003†
K&L grade			
K&L 0	*n* = 11 (17%)	*n* = 18 (40%)	
K&L 1	*n* = 18 (28%)	*n* = 27 (60%)	
K&L 2$^-$	*n* = 5 (8%)		
K&L 2$^+$	*n* = 14(22%)		
K&L 3	*n* = 8 (12.5%)		
K&L 4	*n* = 8 (12.5%)		
Involved compartment			
Medial compartment knee OA	*n* = 30 (47%)		
Lateral compartment knee OA	*n* = 6 (9%)		
Bicompartimental knee OA	*n* = 17 (27%)		
Muscle strength			
Isometric knee extension in 60°, Nm/kg	1.27 (0.34)	1.69 (0.40)	<0.001†
Isometric knee extension in 90°, Nm/kg	1.35 (0.41)	1.76 (0.40)	<0.001†
Isometric knee flexion in 60°, Nm/kg	0.62 (0.19)	0.84 (0.23)	<0.001†
Isometric knee flexion in 90°, Nm/kg	0.53 (0.14)	0.67 (0.16)	<0.001†
Isokinetic knee extension 60°/s, Nm/kg	0.96 (0.34)	1.33 (0.26)	<0.001†
Isokinetic knee extension 240°/s, Nm/kg	0.54 (0.21)	0.72 (0.15)	<0.001†
Pain			
VAS score, 0-100	35 (27)	2 (2)	<0.001†
WOMAC pain score, 0-100	72.7 (18.9)	97.9 (2.7)	<0.001†
Physical performance			
WOMAC function score, 0-100	70.5 (20.0)	98.2 (3.3)	<0.001†
TUG, sec	5.74 (1.24)	5,00 (0.92)	0.001†
SCT, sec	6.24 (1.49)	5.49 (1.07)	0.003†
Pain catastrophizing			
Total Score on PCS, 0-52	16.0 (9.7)	15,2 (9.7)	0.677
Kinesiophobia			
Score on TSK, 17-68	37.1 (5.2)	34.5 (6.1)	0.013†
Pain coping style			
Active coping on PCI, %	57.16 (11.77)	51,99 (11.40)	0.024†
Passive coping on PCI, %	49.00 (10.74)	44.50 (9.65)	0.027†

OA = osteoarthritis; BMI = Body Mass Index; K&L = Kellgren and Lawrence; VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; TUG = Timed Up and Go Test; SCT = Stair Climbing Test; PCS = Pain Catastrophizing Scale; TSK = Tampa Scale for Kinesiophobia; PCI = Pain Coping Inventory

* Data are presented as Mean (SD) or Frequencies (%). The *P* value corresponds to an Independent Samples t-test comparing the two groups.

†Significant difference between groups ($P < 0.05$)

Table 2. Correlation between psychosocial factors and muscle strength, pain and physical performance in 64 subjects with knee OA related symptoms

	Pain catastrophizing (Total score on PCS)		Kinesiophobia (Score on TSK)		Active coping style (Active coping on PCI)		Passive coping style (Passive coping on PCI)	
	r	***P***	***r***	***P***	***r***	***P***	***r***	***P***
Muscle strength								
Isometric knee extension in 60°, Nm/kg	-0.235	0.062	-0.172	0.174	0,221	0,079	0.091	0.474
Isometric knee extension in 90°, Nm/kg	-0.199	0.116	**-0.261**	**0.037***	0.167	0.188	0.058	0.648
Isometric knee flexion in 60°, Nm/kg	**-0.259**	**0.039***	-0.096	0.449	0.057	0.654	0.051	0.688
Isometric knee flexion in 90°, Nm/kg	**-0.309**	**0.013***	-0.114	0.368	0.080	0.532	0.007	0.957
Isokinetic knee extension 60°/s, Nm/kg	-0.073	0.568	-0.122	0.336	0.174	0.170	0.068	0.594
Isokinetic knee extension 240°/s, Nm/kg	-0.026	0.841	-0.051	0.692	0.234	0.065	0.183	0,152
Pain								
VAS score	-0.197	0.118	-0.043	0,734	-0.065	0.610	-0.162	0.200
WOMAC pain score	0.091	0.474	-0.043	0,734	-0.153	0.228	0.048	0.707
Physical performance								
WOMAC function score	-0.011	0.932	-0.106	0.406	-0.061	0.629	0.074	0.559
TUG	0,002	0.986	0.102	0.432	-0.020	0.874	0.033	0.800
SCT	0.035	0.787	0.143	0.267	-0.049	0.706	-0.160	0.215

VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; TUG = Timed Up and Go Test; SCT = Stair Climbing Test; PCS = Pain Catastrophizing Scale; TSK = Tampa Scale for Kinesiophobia; PCI = Pain Coping Inventory

* significant associations based on correlation analysis (Pearson correlation) ($P < 0.05$)

Table 3. Multivariable linear regression analysis: associations between psychosocial factors and isometric muscle strength in 64 knee OA subjects

	Dependent variables											
	Isometric muscle strength, Nm/kg											
	Knee extension 60°			**Knee extension 90°**			**Knee flexion 60°**			**Knee flexion 90°**		
Independent variables	***β***	***P***	***Partial R^2***	***β***	***P***	***Partial R^2***	***β***	***P***	***Partial R^2***	***β***	***P***	***Partial R^2***
Step 1												
Age	-0.004	0.977	0.000	0.048	0.705	0.002	0.128	0.314	0.016	0.124	0.328	0.015
Pain (WOMAC pain)	0.182	0.163	0.032	0.227	0.081	0.049	0.163	0.208	0.025	0.163	0.211	0.025
Structural severity (K&L grade)	-0.010	0.941	0.000	-0.052	0.684	0.003	-0.159	0.210	0.025	-0.188	0.138	0.035
Step 2: Pain Catastrophizing												
Total Score on PCS	**-0.262**	**0.041***	**0.067**	-0.221	0.082	0.048	**-0.259**	**0.040***	**0.065**	**-0.308**	**0.013***	**0.092**
Step 2: Kinesiophobia												
Score on TSK	-0.176	0.176	0.030	**-0.255**	**0.045***	**0.063**	-0.058	0.655	0.003	-0.073	0.568	0.005
Step 2: Pain coping style												
Active Coping on PCI	**0.255**	**0.047***	**0.063**	0.204	0.111	0.040	0.075	0.557	0.005	0.096	0.450	0.009
Passive Coping on PCI	0.096	0.470	0.009	0.043	0.742	0.002	0.003	0.981	0.000	-0.047	0.715	0.002

PCS = Pain Catastrophizing Scale; TSK = Tampa Scale for Kinesiophobia; PCI = Pain Coping Inventory

* significant associations based on regression analysis ($P < 0.05$)

Table 4. Multivariable linear regression analysis: associations between psychosocial factors and isokinetic muscle strength in 64 knee OA subjects

	Dependent variables					
	Isokinetic muscle strength, Nm/kg					
	Knee extension 60°/sec			**Knee extension 240°/sec**		
Independent variables	***β***	***P***	***Partial R^2***	***β***	***P***	***Partial R^2***
Step 1						
Age	0.035	0.783	0.001	-0.010	0.937	0.000
Pain (WOMAC pain)	0.221	0.090	0.046	**0.275**	**0.034***	**0.073**
Structural severity (K&L grade)	-0.167	0.187	0.027	-0.098	0.438	0.009
Step 2: Pain Catastrophizing						
Total Score on PCS	-0.082	0.522	0.006	-0.051	0.692	0.002
Step 2: Kinesiophobia						
Score on TSK	-0.097	0.447	0.009	-0.038	0.767	0.001
Step 2: Pain coping style						
Active Coping on PCI	0.202	0.109	0.040	0.279	0.027	0.075
Passive Coping on PCI	0.040	0.759	0.001	0.179	0.165	0.030

PCS = Pain Catastrophizing Scale; TSK = Tampa Scale for Kinesiophobia; PCI = Pain Coping Inventory

* significant associations based on regression analysis ($P < 0.05$)

Table 5. Multivariable linear regression analysis: associations between psychosocial factors and knee pain and physical performance in 64 knee OA subjects

Independent variables	Dependent variables														
	Pain						Physical performance (subjective)			Physical performance (objective)					
	VAS[a]			WOMAC Pain[a]			WOMAC Function[b]			SCT[b]			TUG[b]		
	β	*P*	*Partial R^2*	*β*	*P*	*Partial R^2*	*β*	*P*	*Partial R^2*	*β*	*P*	*Partial R^2*	*β*	*P*	*Partial R^2*
Pain Catastrophizing															
Total Score on PCS	-0.196	0.125	0.038	0.098	0.444	0.010	-0.037	0.539	0.001	0.027	0.830	0.001	0.002	0.989	0.000
Kinesiophobia															
Score on TSK	-0.040	0.758	0.002	-0.033	0.798	0.001	-0.038	0.519	0.001	0.153	0.206	0.023	0.123	0.318	0.015
Pain coping style															
Active Coping on PCI	-0.067	0.603	0.004	-0.158	0.215	0.025	0.043	0.459	0.002	-0.077	0.531	0.006	-0.054	0.667	0.003
Passive Coping on PCI	-0.169	0.188	0.028	0.037	0.774	0.001	0.017	0.770	0.000	-0.143	0.243	0.019	0.047	0.707	0.002

VAS = Visual Analogue Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SCT = Stair Climbing Test; TUG = Timed Up and Go Test; PCS = Pain Catastrophizing Scale; TSK = Tampa Scale for Kinesiophobia; PCI = Pain Coping Inventory

* significant associations based on regression analysis ($P < 0.05$)

[a] accounting for structural severity (K&L grade) [b] accounting for age, pain (WOMAC pain), BMI and structural severity (K&L grade)

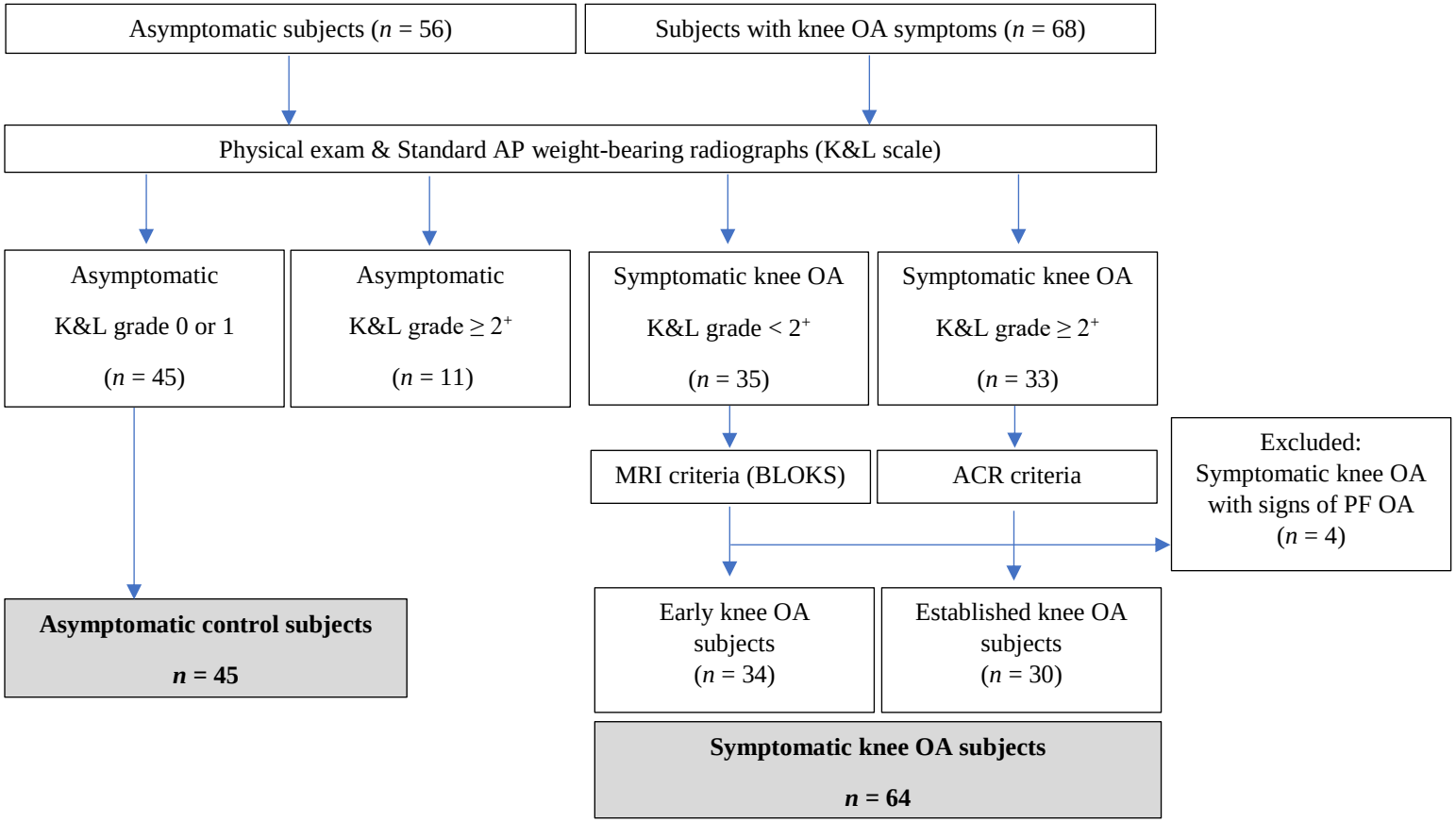

Figure 1. Flowchart showing the selection of the study participants.

OA = osteoarthritis; PF = Patellofemoral; AP = anterior-posterior; K&L = Kellgren and Lawrence; MRI = Magnetic Resoncance Imaging; BLOKS = Boston-Leeds Osteoarthritis Knee Score; ACR = American College of Rheumatology