Multiple psychological factors predict pain and disability among community-dwelling knee osteoarthritis patients: a five-year prospective study

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Objective: To identify predictors of long-term pain and disability in knee osteoarthritis.

Design: A longitudinal cohort study.

Setting: Primary care providers.

Subjects: 108 patients (mean age 63.6, SD 7.2) with knee pain (≥40 mm on a 100-mm visual analogue scale in the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index pain scale) and radiographic grading (Kellgren-Lawrence 2–4) of knee osteoarthritis who participated in a randomized controlled trial.

Main measures: Disease-specific pain and functioning were assessed using the corresponding WOMAC subscales. Generic functioning was assessed by the RAND-36 subscales for function, and physical and mental component summary scores. Possible baseline predictors for these outcomes were 1) demographic and disease-related variables, 2) psychological variables of mood (anxiety, depression), pain-related cognitions (pain self-efficacy, pain catastrophizing, kinesiophobia), and positive resource factors (life satisfaction, sense of coherence).

Results: Multivariate linear mixed model analyses revealed that minimal anxiety at baseline predicted significantly better results for pain (WOMAC p=0.019) and function (WOMAC p=0.001, RAND-36 function p=0.001). High pain self-efficacy predicted significantly better scores in RAND-36 function (p=0.006), physical (p=0.004) and mental (p=0.001) component summaries. Pain catastrophizing predicted higher pain (p=0.015) whereas fear of movement predicted poorer functioning in RAND-36 physical (p=0.016) and mental (p=0.009) component summaries. Those satisfied with life reported higher scores in RAND-36 function (p=0.002) and mental component summary (p=0.041). A low number of comorbidities predicted significantly better results in pain (WOMAC p=0.019) and function (WOMAC p=0.033, RAND-36 p=0.009).

Conclusion: Anxiety, pain-related cognitions and psychological resources predict symptoms in knee osteoarthritis in the long term.

Keywords: Knee osteoarthritis, pain, disability, predictors, psychological factors

Introduction

Traditionally, osteoarthritis has been evaluated from a biomechanical point of view, but there is a growing body of evidence that psychosocial factors have an important role in patients' adjustment to pain.[1-3] The pain perception and disability symptoms among osteoarthritis patients appears to rest upon a complex interaction of factors, including structural damage, peripheral and central pain processing mechanisms, obesity, culture, and demographic and psychosocial factors.[4,5]

There are many cross-sectional studies that report the association of psychological (affective, cognitive, behavioural) variables with pain and disability among knee osteoarthritis patients.[6,7] However, longitudinal studies regarding their predictive role are scarcer. Data from the Osteoarthritis Initiative revealed that baseline depressive symptoms were significantly predictive of worsening in most pain and disability outcomes among knee osteoarthritis patients in a two-year follow-up.[8] Axford et al.[9] reported that greater pain was associated with a reduced ability to cope, increased depression and reduced physical ability in a one-year follow-up study among knee osteoarthritis patients.

Regarding pain-related cognitions pain self-efficacy, pain catastrophizing and kinesiophobia have often been the most studied. A meta-analysis review[10] on pain beliefs and disability among people with arthritis observed highly significant, medium effect sizes for associations between beliefs and problems in functioning. Psychological resources, such as a sense of coherence and life satisfaction, have also been found to be important in dealing with chronic pain and disability, although studies among knee osteoarthritis patients are scarcer. In community-dwelling adults, knee osteoarthritis has been independently associated with lower life satisfaction.[11]

Taken together, several psychosocial variables have been suggested to influence knee osteoarthritis pain and disability. However, there is a shortage of longitudinal studies that have evaluated these factors. To our knowledge previous published studies regarding the predictive role of psychological variables on knee osteoarthritis symptoms have not extended beyond a two-year follow-up. As osteoarthritis symptoms fluctuate by nature, it is essential to measure pain and disability repeatedly over long periods of time to characterise and determine their long-term changes.

In this study we are analysing the five-year follow-up data from a published randomised controlled trial.[12,13] The trial protocol has previously been published.[14]

Patients and methods

The data presented in this article was collected between August 2011 and December 2016 from patients participating in a randomised controlled trial and its five-year follow-up study both conducted at Kuopio University Hospital in Finland. The randomised controlled trial with a one-year follow-up was registered with Current Controlled Trials (ISRCTN64794760) and the Research Ethics Committee of the Hospital District on Northern Savo had approved it (reference number 14/2011). The details of the randomised controlled trial can be found in the protocol paper[14] and its results have been published earlier.[12,13,15] For the five-year follow-up study the ethical approval that was granted by the Research Ethics Committee of the Hospital District of Northern Savo (reference number 344/2016).

We used the set of postal questionnaires in all our follow-up points: baseline, 3 months, 12 months and 5 years. In the five-year follow-up study there were 108 participants, which is three less than in the original trial as two of the patients had wanted to drop out and one other patient had died. Written informed consent was obtained from all patients who participated in the randomised controlled trial as well as the five-year follow-up study. The flow of patients is illustrated in Figure 1.

The outcome measures were self-reported pain and functioning (physical and mental), which were assessed in the following way: Self-reported disease-specific pain and physical functioning were measured with the pain and function subscales (0−100 mm) of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[16,17] using the Finnish validated version[18,19]. The self-reported generic assessments of physical and mental functioning were assessed by the Finnish validated SF-36-item Health Survey RAND-36[20,21] subscales for function and physical and mental component summary scores (0−100) with higher scores indicating better function. For the physical and mental summary scores we decided to calculate the oblique assessments[22] because they incorporate the correlation between the physical and mental component summaries. We used mean and SD values of different RAND-36 subscales in the Finnish population when calculating the component summary scores.[21]

Possible baseline predictors for the outcomes were divided into two groups, thus: 1) demographic, socioeconomic and disease-related variables and 2) psychological measures of mood (anxiety and depression), pain-related cognitions (pain self-efficacy, pain catastrophizing and kinesiophobia), and positive resource factors (life satisfaction, sense of coherence). The baseline predictors were transformed into dichotomous variables before the analyses, except for age, which was treated as a continuous variable.

Demographic, socioeconomic and disease-related variables were age (per 10 years), gender, educational level (comprehensive school vs. upper secondary or vocational school), number of comorbidities, prevalent obesity (normal of overweight with BMI <30.0 kg/m^2 vs. obese with a BMI ≥30.0 kg/m^2), working status (employed vs. retired or unemployed), marital status (cohabiting vs. living alone), radiological grade of knee OA (Kellgren-Lawrence scale 2: minimal vs. 3–4, moderate or severe,[23] duration of knee pain symptoms (<6 (median) vs. ≥6 years), exercise frequency, the group in the randomized controlled trial (CBT intervention vs. control) and time (baseline vs. 3, 12 and 60 months mean). For the transformation to dichotomous variables we used cut off values based on classification systems (BMI, Kellgren-Lawrence scale) or the median of the observations (duration of the hip symptoms). In the case of exercise frequency the cut off value (≥2 times a week vs. ≤1 times a week) was chosen with respect to the recommendations of Physical Activity Guidelines for Americans[24] of strength training at least two times a week. For the number of comorbidities, the cut off (0−2 vs. ≥3) was chosen for acceptable group sizes and clinical relevance.

Depressive symptoms were assessed using the Finnish version of the 21-item Beck Depression Inventory.[25] The cut off point for depression was set at 9/10 with normal mood, scores 0–9 vs. elevated depressions symptoms, scores 10 or more according to the original formulation by Beck and Beamesderfer.[26] The Beck Anxiety Inventory[27] was used to evaluate the severity of symptoms of anxiety with minimal anxiety, scores 0–7 vs. mild anxiety or more, scores 8–63.[27] Pain self-efficacy was assessed with the Finnish version of the Pain Self-Efficacy Questionnaire[28] with scores 41−60 vs. lowest tertile, scores 0−40 and kinesiophobia was evaluated by the Finnish version of the Tampa Scale of Kinesiophobia[29] with scores 0−36 vs. high degree of kinesiophobia, scores 37−68.[30] Pain catastrophizing was evaluated by using the Pain Catastrophizing Scale[31] whereby scores 0−18 were compared against the highest tertile, scores 19−50. Life satisfaction was measured by using a four-item Life Satisfaction scale[32] i.e. satisfied, scores 4−11 vs. dissatisfied, scores 12−20[33,34]).

The sense of coherence was evaluated by using the highly validated 13-item version of the Sense of Coherence[35] scale whereby the scores 68−90 were compared against the lowest tertile, scores 33–67. For the transformation to dichotomous variables we used clinical cut offs defined for each questionnaire when available (Life Satisfaction scale, Tampa Scale of Kinesiophobia, Beck Depression Inventory, Beck Anxiety Inventory). In the case when a cut off had not been defined, for clinically meaningful comparisons we used data-driven tertile grouping (Sense of Coherence, Pain Self-Efficacy Questionnaire, Pain Catastrophizing Scale).

All statistical analyses were performed using SPSS (version 25, SPSS, Chicago, IL, USA). Demographic characteristics and baseline data were summarized by descriptive statistics. According to the power calculations for the original randomized controlled trial[36] 54 patients per group were needed in the comparison of the mean pain scores between the groups.

The associations of possible explanatory variables with the outcome variables were assessed by a multivariate linear mixed model in which the correlation structure of the data due to the multiple measurements (0, 3, 12 and 60 months) could be taken into account. The mixed model has the advantage of using all available data in the analysis, irrespective of whether some data points are missing for a given participant. Separate models were estimated for each outcome. It has been recommended that covariates should be chosen based on their substantive basis and not on a test of differences.[37] Thus, age, gender, educational level, the number of comorbidities, the BMI, work status, marital status and disease severity were included as covariates based on their associations with the study outcomes in prior research.[3,38-40] Finally, a model for demographic, socioeconomic and disease-related variables was fitted of the form, thus:

$Outcome_{0;3;12;60}$ = age + sex + education + comorbidities + BMI + work status + marital status + radiological grade + duration of knee pain + time + randomization + time x randomization.

Similarly, a second model was formulated whereby, depressive and anxiety symptoms, pain self-efficacy, pain catastrophizing, kinesiophobia, life satisfaction and sense of coherence, were included as covariates based on their associations with the study outcomes in prior research.[1,2] Thus, the model for psychological measures was fitted with the following form:

$Outcome_{0;3;12;60}$ = Beck Depression Inventory + Beck Anxiety Inventory + Pain Self-Efficacy Questionnaire + Pain Catastrophizing Scale + Tampa Scale of Kinesiophobia + Life Satisfaction + Sense of Coherence + time + randomization + time x randomization.

The time-by-treatment interaction in both models addresses the question of whether the groups differed in the change between the measurement points. A non-significant time-by-treatment interaction suggests that the changes over the

follow-up period cannot be distinguished from sampling error. Since the time-by-treatment interaction was non-significant in all outcomes, we decided to remove the term from both of the models. Randomization did not show any significance as a covariate in either of the models, one can conclude that it did not have any effect on the outcome variables and could thus have been removed from the mixed model analysis as well. However, we decided to keep it for reasons of clarity.

Results

The baseline characteristics of the study patients are presented in Table 1. The associations of baseline variables (predictors) with the outcome variables are described in Tables 2 and 3.

Multivariate linear mixed model analyses revealed that minimal anxiety at baseline measured by the Beck Anxiety Inventory predicted significantly better results in all of the outcome measures of pain (WOMAC) and function (WOMAC; RAND-36 function, physical and mental component summaries) during the five-year follow-up. Patients with high pain self-efficacy had significantly better scores in measures of general function: RAND-36 function, physical and mental component summaries. High pain catastrophizing predicted significantly higher WOMAC pain levels whereas kinesiophobia predicted poorer functioning in RAND-36 mental and physical component summaries. Those satisfied with life reported higher scores in RAND-36 function and mental component summary. A higher sense of coherence predicted better scores in RAND-36 mental component summary.

Those with fewer comorbidities reported lower WOMAC pain and functional impairment levels and higher scores in the RAND-36 function, physical and mental component summaries. A lower radiological grade predicted better results in the RAND-36 function and physical and mental component summaries. Those exercising more achieved better RAND-36 function scores. Baseline values for WOMAC pain and function and RAND-36 physical component summaries were significantly better than follow-up mean values, a phenomenon demonstrated in several previous studies among osteoarthritis patients.[41]

Discussion

Returning to our original research question of how different disease-specific and psychological variables predict pain and disability among knee osteoarthritis patients, our results can be summarized as three main findings. First, the importance of anxiety symptoms was noteworthy: Minimal anxiety symptoms at baseline had the strongest predictive value for lower

pain, and better disease-specific (WOMAC) and general measures (RAND-36 function, physical and mental component summary scores) of functioning in knee osteoarthritis patients, and the statistical significance of this finding at five-year follow-up grew stronger in comparison to our findings at one-year follow-up.[13] In previous studies the association between anxiety and knee osteoarthritis pain and disability has been well established in cross-sectional study settings.[7,42] However, data from longitudinal studies regarding the predictive role of anxiety in knee osteoarthritis symptoms are scarce and, to our knowledge, do not extending beyond two-year follow-up points.[43,44]

In our study sample, 49% of the patients reported at least mild anxiety symptoms (BAI score of ≥8) and 10% at least moderate symptoms of anxiety (BAI score ≥16). Even though BAI is not a diagnostic instrument, this seems to imply that knee osteoarthritis patients may be prone to anxiety as the prevalence of anxiety disorders in the Finnish population is around only 4%.

Several studies have demonstrated the association[7,45] of depression with knee pain and activity limitations in osteoarthritis. As mentioned earlier, some studies also support the predictive role of depression with symptomatic knee osteoarthritis.[8,44] In our analysis, however, we did not find evidence that depression had any predictive value for self-reported pain or function. This result may have been caused by the low baseline depression levels among our study group, with only 19 patients reporting at least mild depression. This, in turn, may reflect the recruitment process of the original trial as candidates had to take the initiative and show willingness to take part in the study, which is a characteristic that is indicative of less depression.

Second, our results highlight the importance of pain related cognitions (pain self-efficacy, pain catastrophizing and kinesiophobia) as determinants of symptomatic knee osteoarthritis during the five-year follow-up. In particular, our findings regarding the role of pain self-efficacy are marked as it was found to be a significant predictor of all general measures (RAND-36 function, physical and mental component summary scores) of function. Additionally, the statistical significance of this finding grew stronger in comparison to our one-year follow-up data.[13] Previous studies have demonstrated the predictive role of pain self-efficacy regarding the functional ability after total knee replacement.[46] However, our results provide new longitudinal data concerning the impact of pain self-efficacy.

Negatively charged expectations towards pain and function, that is, kinesiophobia and catastarophizing, were also found to be significant determinants of knee osteoarthritis symptoms in the present study. Although kinesiophobia was observed

to predict general function (RAND-36 physical and mental summary score), pain catastrophizing, for its part, predicted knee pain, but not function. With respect to catastrophizing, a systematic review[47] on the psychological factors that affect the outcome on total hip or knee arthroplasty reported strong evidence that patients with pain catastrophizing reported more pain postoperatively. Moreover, cross-sectional analysis on the explanatory value of pain catastrophizing and pain-related fear towards pain and disability have demonstrated similar findings among knee osteoarthritis patients.[48] Our results add to the understanding of the role of negatively charged expectations towards pain and function by providing analysis from a longitudinal study.

Third, the role of positive psychological resource factors such as life satisfaction, and sense of coherence was revealed as determinants of general function during the five-year follow-up. Both life satisfaction and sense of coherence predicted better mental functioning in our analysis whereas those satisfied with life also got significantly higher scores on the RAND-36 function subscale. Similar findings have been reported by White et al.[49] who reported that high positive affect was associated with more daily walking among adults with painful knee osteoarthritis.

Our results are in line with previous findings regarding the impact of comorbidities on knee osteoarthritis symptoms. According to the observations made in a five-year follow-up study by Pisters et al.[50] avoidance of activities, increased pain, greater comorbidity, a higher age, a longer disease duration, and reduced muscle strength and a range of joint motion at baseline predicted more future limitations in activities in knee osteoarthritis patients. Furthermore, a study by Zullig et al.[40] provided evidence that the comorbidity burden, particularly activity-limiting conditions among knee and hip OA patients, was associated with worse patient-related outcomes.

With respect to the weaknesses of this study, there are some points that warrant discussion. Firstly, this was a highly selected population who volunteered to take part in the study: For entering the randomised controlled trial the patients had to have a moderate WOMAC pain subscale level (VAS ≥40/100 mm) and almost half of the study candidates (47%, n = 209) had to be excluded because their WOMAC pain level was too low. Also, the recruitment process may have resulted in the selection of patients who were more active and better off in some aspects of psychological well-being than the average knee osteoarthritis patient. However, in some respects the study sample can be considered representative of ordinary community-dwelling knee osteoarthritis patients, as most of the participants (77%, n = 86) were enrolled in the study as a result of a previous referral to a knee X-ray by their general practitioners. Another weakness of this study is the relatively small number of patients given the large number of variables. Moreover, the impact of the group-based

cognitive-behavioural intervention to the half of the study patients might be considered as a confounding factor. However, we included group randomisation in the mixed model analysis and no significant effects on the outcome variables were found.

In conclusion, the results of the present study revealed that anxiety, pain-related cognitions and psychological resources are important prognostic factors for symptomatic knee osteoarthritis. The question remains as to how to intervene effectively in this variety of psychological risk factors in order to enhance knee osteoarthritis pain status and functional ability. Clearly randomized controlled trials that address both the content and duration of psychological interventions are needed. However, as we are dealing with a common disorder that affects an increasing part of the adult population, interventions can be timely and costly. This is why the question of patient selection is of central importance when studying targeted interventions. As our study sample consisted of both physically and psychologically reasonably healthy individuals, our findings are even more relevant. Thus, there must also be sub-groups of patients in which these psychological variables play an even more significant role in terms of knee osteoarthritis symptoms. The routine assessment of multiple psychological factors in knee osteoarthritis patients could help in identifying these sub-groups of patients who are at risk of elevated pain and disability in the long-term.

Clinical messages

- Minimal anxiety symptoms at baseline had the strongest predictive value for lower pain, and better disease-specific and general functioning in knee osteoarthritis patients during the five-year follow-up.
- High levels of pain self-efficacy at baseline predicted better general functioning during the five-year follow-up.
- Low pain catastrophizing at baseline and few comorbidities predicted significantly lower WOMAC pain scores in knee osteoarthritis patients.

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Author contributions

The authors contributed to the manuscript in the following ways: EE Helminen, JP Arokoski and SH Sinikallio designed the trial protocol; EE Helminen and JP Arokoski were responsible for patient recruitment; EE Helminen drafted the manuscript and statistical analysis; T Selander was the statistical advisor of the study; JP Arokoski and SH Sinikallio revised the manuscript; JP Arokoski and EE Helminen applied for project funding. All authors have read and approved the final manuscript.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Ethical approval

The Research Ethics Committee of the Hospital District of Northern Savo approved the protocol (reference number 344/2016). Written informed consent was obtained from all patients who participated in this study.

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Table 1. Baseline characteristics of the 111 subjects. Data are presented as means (SD) or the number of patients in each group (%).

Age (years) (n = 111)	63.6 (7.2)
Sex, female (n = 111)	77 (69)
Education (n = 110)	
- Junior high or less	34 (31)
- Senior high/vocational school or more	76 (69)
Number of comorbidities (n = 110)	5.1 (3.2)
- 2 or less	28 (26)
- 3 or more	82 (75)
BMI (kg/m^2) (n = 109)	30.0 (6.2)
- Less than 30.0 kg/m^2	65 (60)
- 30.0 kg/m^2 or more	44 (40)
Work status (n = 111)	
- Employed or part time employed	23 (21)
- Retired or unemployed	88 (79)
Marital status (n = 110)	
- Married or cohabiting	37 (34)
- Living alone	73 (66)
Radiological grade, KL (n = 111)	
- KL2	67 (60)
- KL 3–4	43 (40)
Duration of knee pain symptoms (n = 111)	
- Less than 6 years	51 (46)
- 6 years or more	60 (54)
Exercise (n=108)	
- Once a week or less	32 (30)
- 2 times a week or more	76 (70)
Mood (n=111)	
- Beck Depression Inventory score (0–63)	5.9 (4.8)
- Beck Anxiety Inventory score (0–63)	8.1 (6.0)
Pain-related cognitions (n = 111)	
- Pain Self-Efficacy score (0–60)	43.7 (9.8)
- Tampa Scale of Kinesiophobia score (17–68)	34.1 (9.5)
- Pain Catastrophizing Scale score (0–52)	15.2 (11.0)
Positive resource factors (n = 111)	
- Life Satisfaction score (4–20)	7.8 (2.7)
- Sense of coherence score (13–91)	71.6 (12.5)
WOMAC (n = 111)	
- Pain subscale	57.0 (13.4)
- Function subscale	50.7 (19.0)
RAND-36 (0–100)	
- Physical function (n=111)	47.1 (21.5)
- Physical component summary (PCS) (n=103)	40.1 (8.7)
- Mental component summary (MCS) (n=103)	49.9 (8.6)

KL, Kellgren-Lawrence; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (visual analogue scale (VAS), mm); RAND-36, Finnish-validated SF-36-item Health Survey.

Table 2. Changes in WOMAC and RAND-36 parameter estimates (95% confidence intervals) from multivariate linear mixed models with the following explanatory variables (i.e. average differences in outcome variables of knee pain and functioning between groups of categorical predictors).

Parameter	WOMAC pain	WOMAC function	RAND-36 function	RAND-36 PCS	RAND-36 MCS
Age (age divided by 10 years)	−4.16 (−9.57 to 0.86) p=0.125	−4.17 (−10.06 to 1.72) p=0.163	−0.12 (−6.55 to 6.30) p=0.970	0.63 (−2.09 to 3.35) p=0.646	0.30 (−2.53 to 3.13) p=0.836
Sex (male vs. female)	−3.00 (−9.97 to 3.96) p=0.394	−4.48 (−12.29 to 3.33) p=0.258	2.64 (−5.87 to 11.15) p=0.539	1.24 (−2.41 to 4.89) p=0.501	−0.35 (−4.16 to 3.46) p=0.855
Education (junior high vs. senior high or vocational school)	4.26 (−3.07 to 11.58) p=0.252	4.33 (−3.86 to 12.52) p=0.297	−2.00 (−10.90 to 6.91) p=0.657	−2.41 (−6.18 to 1.36) p=0.208	−2.38 (−6.30 to 1.54) p=0.232
Comorbidities (0−2 vs. ≥3)	**−9.48*[a]** **(−17.35 to −1.60)** **p=0.019**	**−9.58*[c]** **(−18.38 to −0.78)** **p=0.033**	**12.86**[e]** **(3.27 to 22.45)** **p=0.009**	**5.95**[h]** **(1.90 to 10.00)** **p=0.004**	**4.25*[j]** **(0.03 to 8.47)** **p=0.048**
BMI (<30.0 vs. ≥30.0 kg/m^2)	−2.36 (−8.86 to 4.13) p=0.472	−3.91 (−11.22 to 3.40) p=0.290	5.97 (−2.02 to 13.96) p=0.141	2.70 (−0.69 to 6.09) p=0.117	2.36 (−1.19 to 5.91) p=0.189
Work status (employed vs. retired/unemployed)	−1.56 (−11.66 to 8.55) p=0.761	−9.96 (−21.08 to 1.17) p=0.079	1.21 (−10.91 to 13.32) p=0.844	0.99 (−4.12 to 6.10) p=0.700	1.54 (−3.78 to 6.86) p=0.566
Marital status (cohabiting vs. living alone)	−1.58 (−9.02 to 5.87) p=0.675	0.87 (−7.48 to 9.23) p=0.836	2.30 (6.81 to 11.42) p=0.617	−0.45 (−4.30 to 3.40) p=0.817	−1.80 (−5.82 to 2.22) p=0.375
Radiological grade (KL 2 vs. KL 3–4)	−3.87 (−10.27 to 2.52) p=0.232	−3.74 (−10.90 to 3.42) p=0.302	**11.22**[f]** **(3.40 to 19.03)** **p=0.005**	**4.36**[i]** **(1.04 to 7.68)** **p=0.011**	**3.75*[k]** **(0.29 to 7.22)** **p=0.034**
Duration of knee pain symptoms (<6 (median) vs. ≥6 years)	1.14 (−5.24 to 7.53) p=0.723	2.25 (−4.91 to 9.42) p=0.533	−6.65 (−14.47 to 1.17) p=0.094	−1.74 (−5.04 to 1.57) p=0.300	−2.38 (−5.84 to 1.07) p=0.174
Exercise (≥2 times a week vs. ≤1 time a week)	−0.40 (−7.12 to 6.32) p=0.906	−6.44 (−13.96 to 1.09) p=0.093	**12.41**[g]** **(4.20 to 20.62)** **p=0.003**	2.47 (−1.01 to 5.96) p=0.161	2.37 (−1.26 to 6.00) p=0.198
Group randomization (CBT intervention n=55 vs. control n=56)	−2.03 (−8.72 to 4.65) p=0.547	0.21 (−7.28 to 7.70) p=0.955	0.78 (−7.40 to 8.95) p=0.851	0.00 (−3.47 to 3.48) p=0.998	−0.29 (−3.91 to 3.34) p=0.875
Time (baseline vs. follow-up average)	**19.85*****[b]** **(15.83 to 23.86)** **p<0.001**	**14.20*****[d]** **(10.31 to 18.09)** **p<0.001**	−1.46 (−5.01 to 2.09) p=0.420	−1.27 (−2.65 to 0.11) p=0.071	0.31 (−0.83 to 1.45) p=0.592

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (visual analogue scale (VAS) mm); RAND-36, Finnish-validated SF-36-item Health Survey; PCS, physical component summary; MCS, mental component summary; KL, Kellgren–Lawrence grade. *P≤0.05; **P≤0.01; ***P≤0.001.

[a]9.48 lower pain score for those with 0−2 comorbidities. [b]19.85 higher pain score at baseline. [c]9.58 lower functional impairment for those with 0−2 comorbidities. [d]14.20 higher functional impairment at baseline. [e]12.86 better physical function for those with 0−2 comorbidities. [f]11.22 better physical function for those with KL2 knee osteoarthritis. [g]12.41 better physical function for those exercising ≥2 times a week. [h]5.95 higher PCS score for those with 0−2 comorbidities. [i]4.36 higher PCS score for those with KL2 knee osteoarthritis. [j]4.25 higher MCS score for those with 0−2 comorbidities. [k]3.75 higher MCS score for those with KL2 knee osteoarthritis.

Table 3. Changes in WOMAC and RAND-36 parameter estimates (95% confidence intervals) from multivariate linear mixed models with the following explanatory variables (i.e. average differences in outcome variables of knee pain and functioning between groups of categorical predictors).

Parameter	WOMAC pain	WOMAC function	RAND-36 function	RAND-36 PCS	RAND-36 MCS
Beck Depression Inventory (normal mood 0–9 n=92 vs. scores 10−63 n=19)	−0.45 (−8.67 to 7.77) p=0.914	−2.68 (−11.61 to 6.25) p=0.553	−4.88 (−14.77 to 5.01) p=0.330	0.15 (−3.79 to 4.09) p=0.941	1.04 (−2.41 to 4.49) p=0.552
Beck Anxiety Inventory (minimal anxiety 0–7 n=58 vs. scores 8–63 n=53)	**−7.41*[a] (−13.57 to −1.26) p=0.019**	**−11.65***[d] (−18.37 to −4.94) p=0.001**	**13.07***[f] (5.64 to 20.51) p=0.001**	**5.95***[i] (3.06 to 8.84) p<0.001**	**6.59***[m] (4.05 to 9.12) p<0.001**
Pain Self-Efficacy Questionnaire score (41−60 n=73 vs. 0−40 (lowest tertile) n=38)	−0.02 (−6.34 to 6.29) p=0.994	−6.81 (−13.67 to 0.05) p=0.052	**10.76**[g] (3.16 to 18.36) p=0.006**	**4.39**[j] (1.40 to 7.38) p=0.004**	**4.39***[n] (1.77 to 7.01) p=0.001**
Pain Catastrophizing Scale score (0−18 n=72 vs. 19−50 (highest tertile) n=39)	**−7.89*[b] (−14.19 to −1.59) p=0.015**	−2.88 (−9.75 to 3.99) p=0.407	−1.70 (−9.31 to 5.91) p=0.658	−0.05 (−3.01 to 2.92) p=0.974	−0.82 (−3.42 to 1.78) p=0.534
Tampa Scale of Kinesiophobia score (0−36 n=75 vs. 37−68 n=36)	−4.87 (−11.20 to 1.46) p=0.130	−6.82 (−13.71 to 0.08) p=0.053	7.33 (0.31 to 14.98) p=0.060	**3.71*[k] (0.70 to 6.72) p=0.016**	**3.56**[o] (0.93 to 6.19) p=0.009**
Life Satisfaction score (satisfied 4−11 n=99 vs. dissatisfied 12−20 n=12)	−1.30 (−11.05 to 8.46) p=0.793	−2.98 (−13.49 to 7.53) p=0.575	**18.23**[h] (6.70 to 29.76) p=0.002**	4.28 (−0.29 to 8.84) p=0.066	**4.17*[p] (0.18 to 8.16) p=0.041**
Sense of Coherence score (68−90 n=72 vs. 33−67 (lowest tertile) n=39)	−1.86 (−8.56 to 4.85) p=0.584	−1.22 (−8.53 to 6.09) p=0.742	0.86 (−7.22 to 8.94) p=0.833	1.68 (−1.59 to 4.95) p=0.311	**3.64*[q] (0.78 to 6.51) p=0.013**
Group randomization (CBT intervention n=55 vs. control n=56)	−1.72 (−7.17 to 3.73) p=0.533	0.88 (−5.04 to 6.80) p=0.769	−0.47 (−7.02 to 6.09) p=0.888	−0.38 (−2.97 to 2.21) p=0.770	−0.30 (−2.57 to 1.97) p=0.795
Time (baseline vs. follow-up average)	**20.39***[c] (16.57 to 24.22) p<0.001**	**14.94***[e] (11.18 to 18.70) p<0.001**	−1.60 (−5.01 to 1.82) p=0.358	**−1.45*[l] (−2.78 to −0.12) p=0.033**	0.21 (−0.87 to 1.29) p=0.701

WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index (visual analogue scale (VAS) mm); RAND-36, Finnish-validated SF-36-item Health Survey; PCS, physical component summary; MCS, mental component summary. *P≤0.05; **P≤0.01; ***P≤0.001.

[a]7.41 lower pain score for those with minimal anxiety symptoms. [b]7.89 lower pain score for those with low Pain Catastrophizing Scale scores. [c]20.39 higher pain score at baseline. [d]11.65 lower functional impairment for those with minimal anxiety symptoms. [e]14.94 higher functional impairment at baseline. [f]13.07 better physical function for those with minimal anxiety symptoms. [g]10.76 better physical function for those with high Pain Self-Efficacy Questionnaire scores. [h]18.23 higher physical function for the satisfied. [i]45.95 higher PCS scores for those with minimal anxiety symptoms. [j]4.39 higher PCS scores for those with high Pain Self-Efficacy Questionnaire scores. [k]3.71 higher PCS scores for those with low Tampa Scale of Kinesiophobia scores. [l]1.45 lower PCS scores at baseline. [m]6.59 higher MCS scores for those with minimal anxiety symptoms. [n]4.39 higher MCS scores for those with high Pain Self-Efficacy Questionnaire scores. [o]3.56 higher MCS scores for those with low Tampa Scale of Kinesiophobia scores. [p]4.17 higher MCS scores for the satisfied. [q]3.64 higher MCS scores for those with high Sense of Coherence scores.

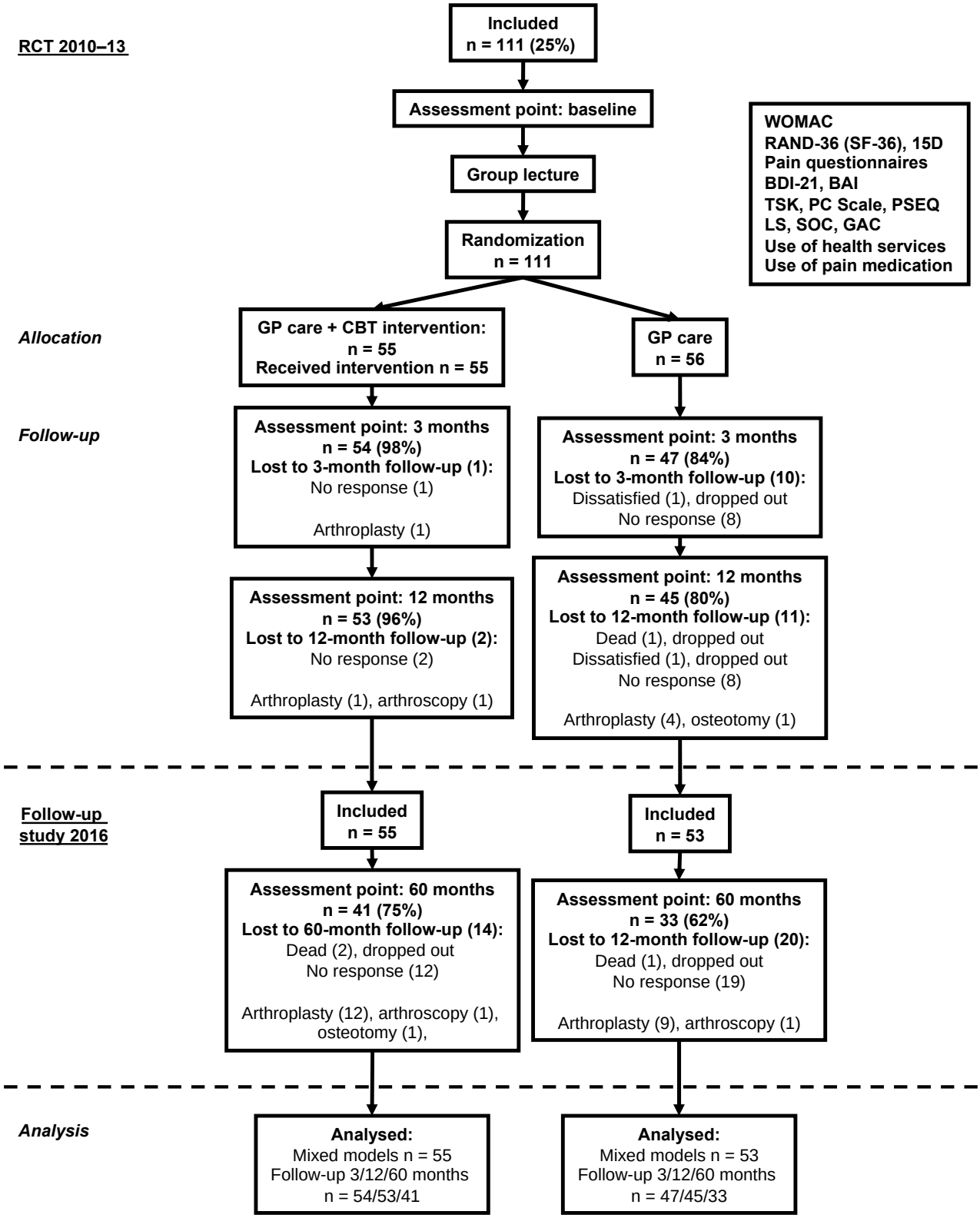
RCT 2010–13
Included
n = 111 (25%)
Assessment point: baseline
Group lecture
Randomization
n = 111
WOMAC
RAND-36 (SF-36), 15D
Pain questionnaires
BDI-21, BAI
TSK, PC Scale, PSEQ
LS, SOC, GAC
Use of health services
Use of pain medication
Allocation
GP care + CBT intervention:
n = 55
Received intervention n = 55
GP care
n = 56
Follow-up
Assessment point: 3 months
n = 54 (98%)
Lost to 3-month follow-up (1):
No response (1)
Arthroplasty (1)
Assessment point: 3 months
n = 47 (84%)
Lost to 3-month follow-up (10):
Dissatisfied (1), dropped out
No response (8)
Assessment point: 12 months
n = 53 (96%)
Lost to 12-month follow-up (2):
No response (2)
Arthroplasty (1), arthroscopy (1)
Assessment point: 12 months
n = 45 (80%)
Lost to 12-month follow-up (11):
Dead (1), dropped out
Dissatisfied (1), dropped out
No response (8)
Arthroplasty (4), osteotomy (1)
Follow-up study 2016
Included
n = 55
Included
n = 53
Assessment point: 60 months
n = 41 (75%)
Lost to 60-month follow-up (14):
Dead (2), dropped out
No response (12)
Arthroplasty (12), arthroscopy (1), osteotomy (1),
Assessment point: 60 months
n = 33 (62%)
Lost to 12-month follow-up (20):
Dead (1), dropped out
No response (19)
Arthroplasty (9), arthroscopy (1)
Analysis
Analysed:
Mixed models n = 55
Follow-up 3/12/60 months
n = 54/53/41
Analysed:
Mixed models n = 53
Follow-up 3/12/60 months
n = 47/45/33

Figure 1. Flow of study patients. RCT = randomized controlled trial; CBT = cognitive-behavioural treatment; WOMAC = Western Ontario and McMaster osteoarthritis index; RAND-36 = the RAND 36-item health survey; 15D = generic 15D instrument; BDI-21 = 21-item Beck Depression Inventory; BAI = Beck Anxiety Index; TSK = Tampa Scale for Kinesiophobia; PCS = Pain Catastrophizing Scale; PSEQ = Pain Self-Efficacy Questionnaire; LS = life satisfaction; SOC = sense of coherence; GAC = global assessment of change.