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Two-year MRI-defined Structural Damage and Patient-Reported Outcomes Following Surgery or Exercise for Meniscal Tears in Young Adults

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SUMMARY BOX

WHAT IS ALREADY KNOWN ON THIS TOPIC

Patients with a meniscal tear are at a higher risk of developing knee osteoarthritis (OA), and surgery to the meniscus might increase the risk of knee OA in patients with degenerative tears. However, the influence of treatment strategy (surgical or non-surgical) on structural knee joint changes and the later risk of knee OA in young patients with meniscal tears is not known.

WHAT THIS STUDY ADDS

Initial treatment strategy (meniscus surgery or supervised exercise and education) did not influence short-term structural knee joint worsening in young adults with meniscal tears, as worsening of structural knee damage on MRI at the two-year follow-up was limited and similar between treatment groups. In addition, early meniscal surgery was not superior to exercise therapy and education with optional delayed surgery in improving patient-reported outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

The findings suggest that both surgical and non-surgical treatment strategies yield similar two-year patient-reported outcomes and structural knee joint changes in young adults with a meniscal tear. Studies on long-term structural damage are needed to investigate long-term knee-joint changes and possible approaches to prevent OA development.

ABSTRACT

Objective To investigate potential differences in structural knee joint damage assessed by MRI and patient-reported outcomes at two-year follow-up between young adults randomized to early surgery or exercise and education with optional delayed surgery for a meniscal tear.

Methods A secondary analysis of a multicenter randomized controlled trial including 121 patients (18–40 years) with an MRI-verified meniscal tear. For this study only patients with two-year follow-up were included. The main outcomes were the difference in worsening of structural knee damage, assessed by MRI using the Anterior Cruciate Ligament OsteoArthrits Score, and the difference in change in the mean score of four Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$) subscales covering pain, symptoms, function in sport and recreation, and quality of life, from baseline to two years.

Results In total, 82/121 (68%) patients completed the two-year follow-up (39 from the surgical group and 43 from the exercise group). MRI-defined cartilage damage had developed or progressed in 7 (9.1%) patients and osteophytes developed in 2 (2.6%) patients. The worsening of structural damage from baseline to two-year follow-up was similar between groups. The mean (95% CI) adjusted differences in change in $KOOS_4$ between intervention groups from baseline to two years was -1.4 (-9.1 to 6.2) points. The mean improvement in $KOOS_4$ was 16.4 (10.4-22.4) in the surgical group and 21.5 (15.0-28.0) in the exercise group. No between group differences in improvement were found in the KOOS subscales.

Conclusions The two-year worsening of MRI-defined structural damage was limited and similar in young adult patients with a meniscal tear treated with surgery or exercise with optional delayed surgery. Both groups had similar clinically-relevant improvements in $KOOS_4$, suggesting the choice

of treatment strategy does not impact two-year structural knee damage or patient-reported outcomes.

Trial Registration ClinicalTrials.gov NCT02995551

Keywords: meniscal tear, MRI, structural changes, osteoarthritis, knee pain, meniscal repair, arthroscopic partial meniscectomy, exercise therapy

INTRODUCTION

Meniscal tears in young adults have typically been treated with arthroscopic surgery. Recently, two randomized trials comparing early meniscal surgery to exercise therapy and education with optional delayed surgery (if needed) reported clinically-relevant improvements in patient-reported outcomes for both treatment strategies, with negligible between-group differences [1, 2]. Furthermore, in the two trials, many patients randomized to exercise (84% at 12 months and 59% at 24 months) did not undergo surgery during follow-up [1, 2].

The risk of developing knee osteoarthritis (OA) is considerably elevated (up to six-fold higher) for knee injury and meniscal tear patients [3, 4]. However, whether the development of structural knee joint changes and the later onset of knee OA is affected by the initial treatment strategy (surgical or non-surgical) in young patients with meniscal tears is unknown. On the one hand, exercise therapy could potentially cause further damage to an already injured joint. On the other hand, arthroscopic partial meniscectomy (APM) has been reported to be associated with an increased risk of Magnetic Resonance Imaging (MRI)-defined cartilage damage [5], a higher risk of developing radiographic knee OA [6], and progression of MRI-defined OA features [7] in middle-aged and older patients with degenerative meniscal tears.

Since OA is the most common joint condition, affecting more than 500 million people worldwide [8], prevention is important to reduce the burden of OA [9, 10]. Thus, knowledge of how treatment strategy impacts structural knee damage and long-term pain and function in young patients is essential as it may help prevent the development of OA.

Therefore, in this secondary analysis of the 'Danish RCT on Exercise vs Arthroscopic Meniscal surgery for young adults (DREAM) trial' – a multicenter RCT comparing two treatment strategies for meniscal tears in young adults [1], we aimed to investigate potential differences in MRI-defined structural knee damage and patient-reported outcomes from baseline to two years in young adults

with meniscal tears treated with either early meniscal surgery or exercise therapy and patient education with optional delayed surgery.

METHODS

Equity, Diversity and Inclusion Statement

Our author team included senior and less-experienced investigators of different genders from various health disciplines. The study population was recruited from public hospitals across Denmark, increasing the results' diversity and generalisability.

Study Design and Participants

This study was a secondary analysis of the 'Danish RCT on Exercise vs Arthroscopic Meniscal surgery for young adults (DREAM) trial'– a multicenter RCT comparing two treatment strategies for meniscal tears in young adults [1]. Participants were recruited from seven orthopeadic departments across Denmark from January 2017 to December 2019. Inclusion criteria were 18-40 years of age, knee pain, clinical history and symptoms consistent with a meniscal tear (confirmed on MRI) and deemed eligible for meniscal surgery (APM or repair) by an orthopeadic surgeon. Inclusion was not limited to traumatic symptom onset, a specific symptom duration or specific types of tears. However, patients with a congenital discoid meniscus or clinical suspicion of displaced bucket handle tear (acute locking of the knee or extension deficit) confirmed on MRI were excluded. If there were no symptoms from acute locking of the knee, all types of tears were included. Other exclusion criteria were prior surgery of the affected knee, fracture of the affected extremity in the previous 12 months, complete rupture of any knee ligament or participation in supervised exercise therapy within the last three months. The participants were followed up at 3, 6 and 12 months with online questionnaires. Patients consenting to participate in the two-year MRI

follow-up assessment also received a two-year follow-up questionnaire. In this study, we only included participants with two-year follow-ups.

Interventions

Patients randomly assigned to receive meniscal surgery underwent APM or meniscal repair. The operating surgeon determined the type of surgery to increase generalizability to clinical practice. Patients allocated to exercise therapy and patient education participated in a 12-week program consisting of twice-weekly supervised exercise sessions. Patient education was delivered at the beginning and the end of the program by trained physical therapists [11]. Detail of the program is presented in the study protocol [12].

Patients and public involvement

Patients and clinicians were involved in the development of the design of the intervention as described in the pilot paper [11] but not in the planning of this secondary analysis.

Outcomes

MRI

Baseline and two-year follow-up MRIs were performed with a minimum of a 1.5-T scanner using the individual radiology departments' protocol for suspected meniscal tears. All protocols included sagittal, axial, and coronal sequences with and without fat suppression. The main outcomes were the between-group difference in worsening in MRI-defined structural damage (i.e., new or progressed cartilage damage, osteochondral damage, and osteophytes) from baseline to 24 months, assessed using a slightly modified Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS) [13]. ACLOAS is a semiquantitative MRI-based scoring system that includes structural features relevant to acute injury, degenerative incident features, and longitudinal follow-up of structural OA

features. Cartilage damage is scored from 0 to 6 in 14 subregions. Osteochondral damage is scored from 0 to 4 in 14 subregions, and osteophytes are scored from 0 to 7 in 12 locations. The scores for cartilage damage, osteochondral damage, and osteophytes were summed on the knee level. Thus, the worsening of individual MRI features includes new or progressed damage in one subregion and progression in the number of subregions affected. We did not include meniscal damage worsening in this study since one of the interventions (APM) specifically altered the meniscus morphology.

We also assessed for any bone marrow lesion (BML), knee joint effusion/synovitis, and anterior cruciate ligament and collateral ligament status. A BML was defined as a reticular ill-defined hyperintense lesion on water sensitive fat suppressed sequences and was scored in 15 subregions (present/absent), and summed on the knee level. Effusion/synovitis or surrogates for this were scored in two locations: capsular distension in the suprapatellar recess (0 to 3) and signal alterations in Hoffa´s fat pad (0 to 3). Since effusion is often located in other recesses beside the suprapatellar recess, we added an assessment of overall effusion/synovitis, including all recesses. We used it as the primary effusion/synovitis score. Furthermore, we recorded the presence of Baker's cysts and any possible change for overall effusion/synovitis and Baker's cysts (decreased, unchanged, increased). An experienced musculoskeletal (MSK) radiologist (DR) scored all the MRI scans, blinded to clinical information. The baseline and follow-up MRIs were assessed pairwise and unblinded to the sequence to maximize sensitivity to detect change [14]. We assessed inter-rater reliability by another experienced MSK radiologist (EK) independently reading 20% of the scans. Both MRI assessors were trained and supervised by a third experienced professor in MSK radiology (MB) to reach a consensus before the scoring. The overall percentage of agreement and Prevalence And Bias Adjusted Kappa were calculated, except for the meniscal damage, where we used weighted Kappa due to the high prevalence of lesions (all had lesions). Most scores had an inter-

rater agreement of >95%, and the reliability was substantial (range, 0.61–0.8) or almost perfect (range, 0.81–1.0) according to the interpretation by Landis and Koch [15].

Patient-reported outcomes

We assessed the between-group difference in change in the mean score of the Knee Injury and Osteoarthritis Outcome Scores ($KOOS_4$) from baseline to two years (i.e. primary outcome in the main study). The $KOOS_4$ is the mean of four of five subscale scores, including pain, symptoms, function in sport and recreation, and quality of life, and ranges from 0 to 100, with lower scores indicating worse symptoms, function, and quality of life [16, 17]. Additional patient-reported outcomes were the between-group difference in change in the individual KOOS subscales and the Western Ontario Meniscal Evaluation Tool (WOMET), a meniscus-specific, valid, and reliable patient-reported outcome measure (converted to scores from 0 to 100, with lower scores indicating a worse quality of life) [18, 19].

Statistical Analysis

We used descriptive statistics to describe baseline characteristics and frequencies of MRI features. We conducted all analyses according to the intention-to-treat principle, with patients distributed according to the treatment arm they were randomized to (irrespective of the treatment received). In addition, an as-treated analysis was performed. In this analysis, the patients undergoing meniscal surgery up until two years follow-up were included in one group. Those undergoing exercise and education (irrespective of their compliance with the exercise), who had not received delayed surgery, were included in the other group. Chi-square or Fisher's exact test, as appropriate, was used to compare the frequency of participants with MRI-worsening between groups. A detailed analysis of the distribution of ACLOAS grades between the groups was irrelevant since the number and severity of the findings were low.

For the patient-reported outcomes, we used the same analytical approach as in the primary reporting of the DREAM study [1]: A linear mixed model with time (baseline, 3, 6, 12 and 24 months as discrete variables), treatment group (surgery or exercise), and the interaction between time and treatment group as fixed effects constraining the difference between the arms to 0 at baseline (i.e., adjusting for baseline imbalance). The model was adjusted for the randomization stratification factors (centre and sex) and age. A patient-specific intercept and slope were added as random effects to accommodate within-person measurement dependence. A common error variance was assumed for all follow-up time points and treatment arms, although error variance can differ at baseline. The assumptions for model validity were checked using scatter plots of the residuals versus time and two dimensional scatterplots of the BLUPs (Best Linear Unbiased Prediction) of the random effects. A 95% confidence interval (CI) excluding 10 points or more in $KOOS_4$ was interpreted as no clinically meaningful difference. No imputation was performed as the mixed model included all patients [20]. All statistical analyses were performed using Stata 17.0 (StataCorp, College Station, TX, USA).

RESULTS

Of 121 patients randomized, 82 (68%) consented to participate in the two-year follow-up (39 from the surgical group and 43 from the exercise group). After several attempts to contact patients or reschedule appointments for MRI scans, 78 provided patient-reported outcomes (PROMS), and 77 provided MRI data. Thus, nine patients only had either the MRI or the PROMS data. Baseline characteristics were similar between patients participating in the follow-up and those who did not (Supplementary file, Table S1). The mean time (SD) from baseline to two-year follow-up was 28 months (4.4). The patients' mean age (SD) at baseline was 29.5 (6.6). About a quarter were female;

most patients were active and had a symptom duration of 0 to 12 months and a traumatic or semi-traumatic symptom onset. Overall, baseline characteristics in the two groups were similar, except for age and slightly better KOOS scores at baseline in the surgery group compared with the exercise and education group (Table 1). This imbalance was consistent with the primary report of the DREAM study [1].

At 12 months follow-up, 16 of the 61 patients (26%) randomly assigned to exercise and education had crossed over to surgery. Between 12 and 24 months, two additional patients from the exercise and education group had knee surgery, while four in the surgical group had a second knee surgery (Figure 1). None of the participants reported any contact with general practitioners or hospitals due to a new knee injury between 12 months to two-year follow-ups.

Baseline MRI findings

Baseline findings are summarized in Table 1. Of the meniscal tears, 65% (n=53) were isolated medial, 30% (n=25) isolated lateral, and 4% (n=3) had both medial and lateral tears. For medial meniscal tears, 34% (n=28) were bucket-handle or complex followed by 26% (n=21) horizontal, whereas radial and vertical tears were the most frequent lateral tears, 15% (n=12). There was no essential difference in the type of tears between the groups assessed with ACLOAS. In one participant (1%), the baseline scan was described without a meniscal tear. However, since the patient was included in the study, the clinical MRI report and the including surgeon must have assessed the scan differently, and thus we decided to also include the patient in this secondary analysis. Besides meniscal tears, there were few MRI-defined baseline changes with a similar distribution between groups. One patient fulfilled suggested criteria for MRI-defined OA [21, 22]. Seven patients had anterior cruciate ligament (ACL) or medial collateral ligament (MCL) changes, all related to mild sprains. The most common baseline MRI findings were knee joint

effusion/synovitis (n=39), Hoffa synovitis (n=21), and bone marrow lesions (edema) (n=16) (Table 1).

MRI-defined Damage Worsening

Cartilage damage worsening was observed in 9% (n=7) of all patients with MRI and osteophytes in 3% (n=2) of patients. Details of the type of worsening (progression in one subregion or in regions affected are listed in supplementary Table S2). Still, only one patient had MRI-defined OA [21, 22]. We observed similar worsening of cartilage damage (p=1.000) and osteophytes (p=0.203) between treatment arms, and in the as-treated analyses. BML, knee effusion/synovitis, Hoffa synovitis, and Baker's cysts were unchanged in 73-90% of the patients and here too we found no essential differences between the groups for these findings (Table 2).

Patient-Reported Outcomes

We observed no essential difference in change between groups from baseline to two years in $KOOS_4$ (Table 3). The mean crude and adjusted between-group differences in change were -5.1 (95% CI -13.8 to 3.7) and -1.4 (95% CI -9.1 to 6.2) points (in favour of the exercise group), respectively. On average, most of the improvement was observed during the first six months of the trial. At two-years the surgical group had improved by 16.4 (95% CI, 10.4 to 22.0), while the exercise group had improved by 21.5 (95% CI, 15.0 to 28.0). The individual KOOS subscales yielded similar results (Table 3). For the WOMET, these improvements were 20.2 (95% CI 12.9 to 27.5) for the surgery group and 26.7 (95% CI 18.6 to 34.8) for the exercise and education group, with an adjusted between-group difference in change of -2.4 (95% CI -11.8 to 6.9) from baseline to two years (Table 3). Likewise, the as-treated analyses yielded no essential between-group differences in change (Fig. 2B; Supplementary table S3).

DISCUSSION

We found that the risk of two-year worsening of structural damage was low and similar in patients undergoing early surgery and patients undergoing exercise and education with optional delayed surgery. Likewise, the as-treated analysis comparing early or delayed surgery to exercise and education did not reveal any essential differences. Moreover, we found that early surgery was not superior to a strategy of exercise and education with optional delayed surgery in improving pain, function, and quality of life at two years, similar to the 12-month results [1].

Our study, including young patients, found less structural worsening over two years than in previous studies, including older patients with degenerative meniscal tears [6, 7, 23]. Moreover, in contrast to an earlier trial comparing APM with physiotherapy for degenerative meniscal tears in older patients with radiographic knee OA that reported significantly greater MRI-defined worsening of cartilage damage and osteophytes in the APM group compared to the exercise group [23], we did not detect a difference between groups. Whether the previous finding of more severe structural worsening in knees with OA relates to patients' age, the degree of structural damage at baseline or other factors, like the type of meniscal repair or resection, tear/injury or symptom onset, is unknown. Most patients (80%) in our study had traumatic or semi-traumatic symptom onset. However, subgroup differences can exist for those with gradual onset that are most likely degenerative tears. Regarding the influence of age, Roos et al. [24] reported that for patients who sustained an isolated meniscus injury between the ages of 17 and 30, the average time until the development of radiologic signs of OA (on radiographs) was about 15 years. In contrast, the corresponding time interval was only about five years for those over age 30 with the same injury, indicating a strong association between age and the worsening of structural damage.

Comparing the structural worsening in our study to studies of young patients with ACL injuries, we find differences that indicate an association between the baseline damage and worsening (short or long-term). The ACL studies [25, 26] report more severe structural baseline knee damage (e.g., cartilage and osteochondral lesions) and more structural worsening over time than our study, where the participants had isolated meniscal tears.

Recent systematic reviews report no additional clinically relevant benefit of APM over placebo surgery or exercise therapy in middle-aged and older adults with degenerative meniscal tears [27-29]. Based on this evidence, clinical guidelines generally recommend against arthroscopic surgery and recommend non-surgical treatment for older patients with degenerative tears [28]. However, young patients with meniscal tears are usually offered surgery [30]. This secondary analysis of the two-year outcome from the DREAM trial [1] confirms the primary 12-month reporting and yields similar results as the two-year reporting from the STARR trial [2]. Early surgery was not superior to exercise and education, with optional delayed surgery for treating isolated meniscal tears in young adults.

Limitations

Thirty-two percent of patients were lost to follow-up. Although we performed analyses according to the intention-to-treat principle, the assumption of including all patients was violated. The resulting direction of this bias is unknown. Nevertheless, we observed no difference in baseline characteristics between patients participating and those lost to the two-year follow-up. Also, the as-treated analyses should be interpreted with caution due to the low number of patients in each group in these analyses. The MRI scans were conducted at seven different departments, which may result in a difference in the visualization of the findings between the departments. Since our primary MRI

outcome was worsening structural damage, the scans were assessed pairwise and unblinded to the sequence to maximize sensitivity for change [15], mitigating some variations caused by differences between departments.

Clinical and research implications

These findings suggest that both treatment strategies are equally effective in relieving symptoms in young patients and highlight the importance of including the patient's treatment preferences when deciding on a treatment strategy. Specific tear types may benefit more from one treatment than the other, but future studies on effect modification are needed to provide more insight into this important clinical issue. Moreover, studies with longer follow-ups are needed to investigate long-term knee joint changes and possible approaches to prevent OA development.

CONCLUSION

Our results suggest that in young adults treated for isolated meniscal tears the two-year worsening of MRI-defined structural damage indicative of knee OA is low and similar between treatment strategies (early surgery vs. exercise with the option of later surgery). In addition, early meniscal surgery is not superior to exercise and education in improving two-year patient-reported outcomes. These findings are important in the decision-making between patients and clinicians on the treatment choice, as both strategies appear viable.

ARTICLE INFORMATION

Achnowledment: The DREAM study group **(**A complete list of contributors to the DREAM Study Group is provided in Supplementary file).

Author Contributions:

Responsible author: S Clausen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: ST Skou, M Boesen, P Hölmich, M Englund, JB Thorlund

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: S Clausen and JB Thorlund

Critical revision of the manuscript for important intellectual content: All authors

Statistical analysis: S Clausen and C Damsted

Obtained funding: JB Thorlund and ST Skou

Conflict of Interest Disclosures:

S.T. Skou has received personal fees from Munksgaard, TrustMe-Ed and Nestlé Health Science, outside the submitted work, and is co-founder of Good Life with osteoArthritis in Denmark (GLA:D®), a not-for profit initiative hosted at University of Southern Denmark aimed at implementing clinical guidelines for osteoarthritis in clinical practice.

Dr. Thorlund report a research grant from Pfizer outside the submitted work (completed in 2022).

CV reports no conflict of interest in this study. Outside submitted work CV received travel expences from Stryker.

Other authors: no conflict of interest.

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Ringsted Hospitals, and Region Zealand (Exercise First program grant). The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

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Figure 1 Flow of study participants.

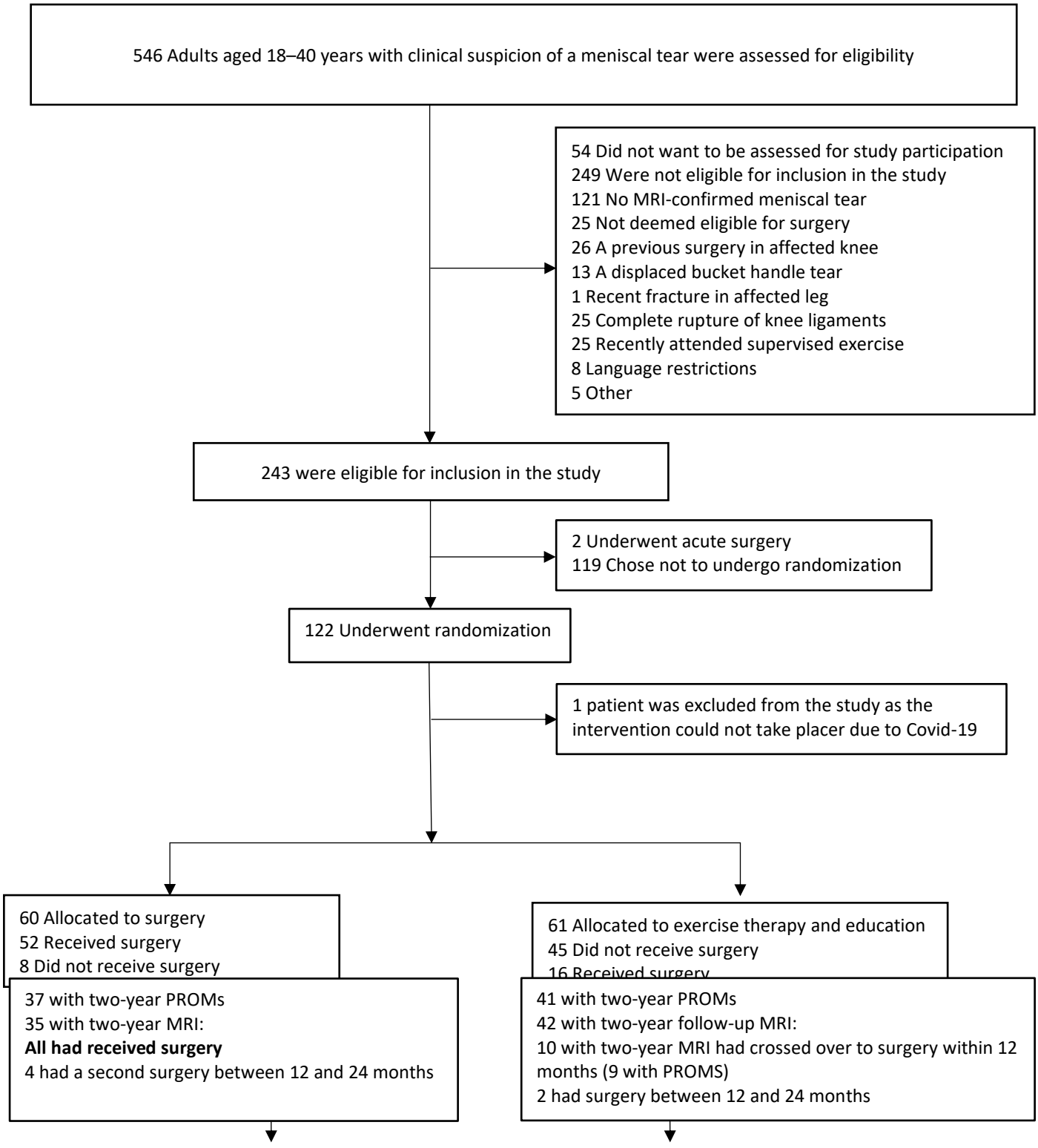
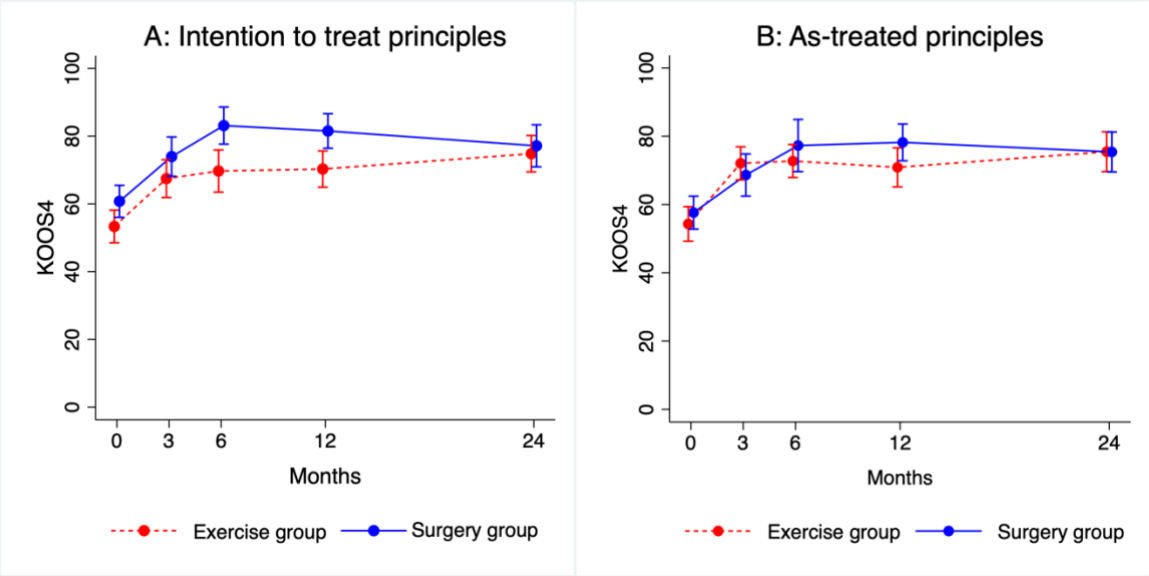


Figure 2. Mean Unadjusted Knee Injury and Osteoarthritis Outcome Scores.



A: Patients distributed according to the treatment arm they were randomized to (irrespective of the treatment received).

B: In this analysis, the patients undergoing surgery up until two years follow-up were included in the surgery group. Those undergoing exercise and education (irrespective of their compliance with the exercise) who had not received delayed surgery constituted the other group.

The error bars indicate 95% CIs.

Table 1. Baseline characteristics of the DREAM-participants with two-year follow-up

	With two-year follow-up	
	Surgical group (n=39)	**Exercise group (n=43)**
Female sex, n (%)	11 (28)	11 (26)
Age (years), mean (SD)	27.8 (6)	31.1 (7)
BMI[a], mean (SD)	25.4 (4)	26.1 (5)
Tegner Activity Scale before injury[b], median (IQR)	6 (5 – 8.5)	5 (4 – 7)
Symptom duration, n (%)		
0-3 months	6 (15)	10 (23)
4-6 months	16 (41)	13 (30)
7-12 months	7 (18)	10 (23)
13-24 months	5 (13)	3 (7)
Longer than 24 months	5 (13)	7 (16)
Symptom onset, n (%)		
Slowly evolved over time	8 (20.5)	11 (25.6)
Semi-traumatic	16 (41.0)	19 (44.2)
Traumatic	15 (38.5)	13 (30.2)
KOOS scores[c], mean (SD)		
$KOOS_4$ (0-100)	60.7 (14)	53.8 (16)
Pain (0-100)	70.4 (15)	64.1 (17)
Symptoms (0-100)	71.8 (16)	70.3 (17)
Activities of daily living (0-100)	79.7 (16)	75.9 (18)
Quality of life (0-100)	51.3 (16)	42.2 (18)
Function in sport and rec. (0-100)	49.4 (23)	38.7 (23)
WOMET summary score (0-100) [d], mean (SD)	49.2 (19)	41.7 (18)
Baseline MRI findings*		
Medial meniscal tear, n (%)	26 (67)	30 (70)
Horizontal tear	11 (28)	10 (23)
Radial and vertical tear	2 (5)	5 (12)
Bucket-handle or complex tear	13 (33)	15 (35)
Lateral meniscal tear, n (%)	14 (36)	14 (33)
Horizontal tear	3 (8)	4 (9)
Radial and vertical tear	6 (1)	6 (14)
Bucket-handle or complex tear	5 (13)	4 (9)
Anterior cruciate ligament (ACL) changes, n (%)	1 (3)	2 (5)
Medial collateral ligament (MCL) changes, n (%)	1 (3)	3 (7)
Lateral collateral ligament changes[e] (LCL), n (%)	0 (0)	0 (0)
Cartilage damage, n (%)		
Femur	0 (0)	0 (0)
Tibia	0 (0)	0 (0)
Patella	3 (8)	3 (7)
Osteochondral damage, n (%)	0 (0)	0 (0)
Osteophytes (one or more locations), n (%)	2 (5)	0 (0)

Bone Marrow Lesions, n (%)	7 (18)	9 (21)
Knee joint effusion/synovitis, n (%)	18 (46)	21 (49)
Bakes cyst, n (%)	8 (21)	3 (7)
Hoffa synovitis, n (%)	7 (18)	14 (33)

Note: Values are presented as number of patients (n) (%), mean (SD), or median (interquartile range).

[a]The Body Mass Index calculated as the weight in kilograms divided by the square of the height in meters.

[b]Tegner Activity Scale (ranging from 0-10; 0 being sick leave or disability pension because of knee problems and 10 being competitive sports: European football (national and international elite level)

[c]KOOS: Knee injury and Osteoarthritis Outcome Score and its subscales Pain, Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and Quality of life (QOL) have scores ranging from 0 (worst) to 100 (best). $KOOS_4$ is the mean score of four out of five of the KOOS subscale scores, i.e. Pain, Symptoms, Sport/Rec and QOL.

[d]WOMET: Western Ontario Meniscal Evaluation Tool (converted into 0-100; lower scores indicating worse quality of life).

*Assessed using Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS).

[e]All changes were related to mild sprain e.g., thickened, or high intra-ligamentous signal of ACL or fluid around the MCL.

Table 2 MRI-defined* changes from baseline to two-year follow-up

	Main analysis**			As-treated analysis		
	Surgical group (n=35)	**Exercise group (n=42)**	**P-value[#]**	**Surgical group (n=47)**	**Exercise group (n=30)**	**P-value[#]**
Cartilage damage, n (%)						
Worsening	3 (9)	4 (10)	1.000	4 (9)	3 (10)	1.000
Osteochondral damage, n (%)						
Worsening	none	none		none	none	
Osteophytes, n (%)						
Worsening	2 (6)	0 (0)	0.203	2 (4)	0 (0)	0.508
Bone marrow lesions, n (%)						
Worsening	2 (6)	3 (7)		3 (6)	2 (7)	
Decreased or disapeared	4 (11)	8 (19)		6 (13)	6 (20)	
No change	29 (83)	31 (74)	0.702	38 (81)	22 (73)	0.761
Intraarticular effusion/synovitis, n (%)						
Worsening	2 (6)	1 (2)		3 (6)	0 (0)	
Decreased or disapeared	4 (11)	6 (14)		4 (9)	6 (20)	
No change	29 (83)	35 (83)	0.793	40 (85)	24 (80)	0.202
Hoffa synovitis, n (%)						
Worsening	3 (9)	2 (5)		3 (6)	2 (7)	
Decreased or disapeared	4 (11)	6 (14)		4 (9)	6 (20)	
No change	28 (80)	34 (81)	0.83	40 (85)	22 (73)	0.359
Baker's cyst, n (%)						
Worsening	3 (9)	1 (2)		3 (6)	1 (3)	
Decreased or disapeared	3 (9)	3 (7)		4 (9)	2 (7)	
No change	29 (83)	38 (91)	0.526	40 (85)	27 (90)	1.000

Note: Values are numbers of participants, with percentages in parentheses

* Assessed using Anterior Cruciate Ligament OsteoArthritis Score (ACLOAS)

**Analyzed according to the randomization group, irrespective of received treatment or cross-over.

[#]Fisher's exact test

Table 3 Patient Reported Outcomes at two-year follow-up (main analysis)

Outcome	**Mean improvement from baseline to two-year follow-up** (95% CI)		**Between-group difference in mean improvement** (95% CI)	
	Meniscal surgery group (n=37)	**Exercise and education group (n=41)**	**Crude**	**Adjusted[c]**
Primary				
$KOOS_4$ [a,b]	16.4 (10.4, 22.4)	21.5 (15.0, 28.0)	-5.1 (-13.8, 3.7)	-1.4 (-9.1, 6.4)
Secondary				
KOOS[a] subscale scores				
Pain	16.1 (9.7, 22.6)	19.2 (13.1, 25.2)	-3.0 (-11.7, 5.7)	1.5 (-5.2, 8.1)
Symptoms	10.5 (4.2, 16.9)	15.3 (10.1, 20.4)	-4.7 (-12.7, 3.2)	-2.9 (-9.0, 3.2)
ADL	10.5 (5.8, 15.3)	14.7 (9.3, 20.2)	-4.2 (-11.4, 2.9)	-1.5 (-6.8, 3.8)
Sport/Rec	22.2 (12.6, 31.7)	30.0 (20.0, 40.0)	-7.8 (-21.5, 5.9)	-1.7 (-13.1, 9.7)
QOL	16.7 (10.3, 23.1)	21.5 (13.5, 29.5)	-4.7 (-15.0, 5.5)	-0.5 (-9.9, 10.0)
WOMET[d] score	20.2 (12.9, 27.5)	26.7 (18.6, 34.8)	-6.5 (-17.3, 4.2)	-2.4 (-11.8, 6.9)

*Adjusted for the randomization stratification factors (center and sex) and age.

[a]KOOS: Knee injury and Osteoarthritis Outcome Score and its subscales Pain, Symptoms, Function in daily living (ADL), Function in sport and recreation (Sport/Rec) and Quality of life (QOL) have scores ranging from 0 (worst) to 100 (best). $KOOS_4$ is the mean score of four out of five of the KOOS subscale scores, i.e., Pain, Symptoms, Sport/Rec and QOL. Improvements of 10 points or more are considered clinically relevant.

[b]Of 390 possible data points (5 time points x 78 patients) 23 data points were missing.

[c]Adjusted for the randomization stratification factors (center and sex) and age.

[d]WOMET: Western Ontario Meniscal Evaluation Tool (converted into 0-100; lower scores indicating worse quality of life). For WOMET we had n=34 in both groups.