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Physical Activity Is Related with Cartilage Quality in Women with Knee Osteoarthritis

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Abstract

Purpose: To study the relationship between 12-month leisure-time physical activity (LTPA) level and changes in estimated biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis (OA). **Methods:** Originally 87 volunteer postmenopausal women, aged 60-68 years, with mild knee OA (Kellgren Lawrence I/II and knee pain) participated in a randomised controlled, 4-month aquatic training trial (RCT), after which 76 completed the 12-month post-intervention follow-up period. Self-reported LTPA was collected along the 12-month period using a diary from which metabolic equivalent task hours (MET_h) per month were calculated. Participants were divided into MET_h tertiles: 1=lowest (n=25), 2=middle (n=25) and 3=highest (n=26). The biochemical composition of the cartilage was estimated using transverse relaxation time (T₂) mapping sensitive to the properties of the collagen network and delayed gadolinium-enhanced magnetic resonance imaging of the cartilage (dGEMRIC index) sensitive to the cartilage glycosaminoglycan (GAG) content. Secondary outcomes were cardiorespiratory fitness, isometric knee extension and flexion force and the knee injury and osteoarthritis outcome questionnaire (KOOS). **Results:** During the 12-month follow-up period, there was a significant linear relationship between higher LTPA level and increased dGEMRIC index changes in the posterior region of interest (ROI) of the lateral (p=0.003 for linearity) and medial (p=0.006) femoral cartilage. Furthermore, these changes were seen in the posterior lateral femoral cartilage superficial (p=0.004) and deep (p=0.007) ROIs and in the posterior medial superficial ROI (p<0.001). There was no linear relationship between LTPA level and other measured variables. **Conclusions:** These results suggest that higher LTPA level is related to regional increases in estimated GAG content of tibiofemoral cartilage in

postmenopausal women with mild knee OA as measured with dGEMRIC index during a 12-month period.

Key Words: Cartilage composition; Leisure-time physical activity; MET; Quantitative magnetic resonance imaging; Postmenopausal women; Follow-up study

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INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of pain and disability (11) and has significant socio-economical costs globally as it accounts for 83% of the total OA burden (36). Early OA causes changes in the biochemical composition of cartilage, such as loss of integrity of the collagen matrix and decrease in glycosaminoglycan (GAG) content (6). There is no known cure for OA, and thus, the main goal of OA management is pain relief and improving physical function (20). Therapeutic exercise, either land- or water-based, has been shown to evoke acute positive post-treatment effects on these goals (5, 39). However, while the effects of therapeutic exercise on pain are lost six months after the cessation of the exercise, small but significant improvements in self-reported physical function are sustained up to 24 months (5).

Active lifestyle with exercise has been shown to be beneficial for the maintenance of the biomechanical properties of cartilage both in healthy humans (31, 32, 34) and animals (13, 14). Thus, physical activity could be effective for the maintenance of cartilage health. Studies of the immediate post-treatment effects of exercise interventions on human cartilage are sparse, but show that the loading created by the exercise interventions can improve the estimated biochemical composition of tibiofemoral (24, 28) and patellofemoral (16) cartilage. In addition to positive cartilage responses observed in these studies (16, 24, 28), impact (16, 23), aquatic (24) and neuromuscular (28) exercise is shown not to be harmful for the estimated biochemical composition of the knee articular cartilage in population with mild knee OA (16, 23, 24) or at high risk of developing knee OA (28). Also, exercise is well tolerated in these populations (16, 23, 24, 28). Furthermore, Teichtal *et al.* (31) observed in a longitudinal follow-up study with

healthy population that over two years of vigorous physical activity is associated with a reduced rate of patella cartilage loss and has a trend towards a reduced risk for worsening patella cartilage defects.

In osteoarthritic population, there are no known long-term follow-up studies investigating the relationship between knee articular cartilage and LTPA. Therefore, the aim of the present study was to investigate the relationship between 12-months of LTPA and the biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis.

METHODS

Study design

This study was a 12-month follow-up to our previously reported 4-month registered randomised controlled trial (ISRCTN65346593) with two experimental arms: 1) aquatic resistance training and 2) control (24). Therefore, the term “original intervention” is used to mean the period of 4-month RCT and “follow-up” denotes to the 12-month period after the end of the intervention and is the focus of the current study. This analysis, which exploited the data from the previous intervention study, followed the published protocol without changes (38). The participants were women aged 60-68 years with mild knee OA and were divided into tertiles based on their average monthly LTPA (METH) during the follow-up period. The study protocol (Dnro 19U/2011) was approved by the Ethics Committee of the Central Finland Health Care District and conforms to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Study participants

Originally, postmenopausal women experiencing knee pain on most days from the Jyväskylä region in Central Finland were voluntarily recruited through advertisements in local newspapers. Preliminary eligibility to the original intervention was assessed using a structured telephone interview (n=323), followed by evaluation of osteoarthritis severity in the tibiofemoral joint with radiographs (confirmed mild tibiofemoral joint OA grades I or II according to the Kellgren Lawrence classification) (n=180) and finally through medical screening (n=111). In total 87 participants were included in the original intervention study. Inclusion criteria to the original intervention were: 1) a postmenopausal woman aged 60-68 years, 2) experiencing knee pain on most days, 3) participating in no more intensive exercise than brisk walking \leq twice a week, 4) radiographic changes in tibiofemoral joint K/L I or II, 5) no cancer or chemotherapy prior to the study, 6) no medical contraindications or other limitations to full participation in an intensive aquatic training program and 7) complete T2 data. Exclusion criteria included: 1) a T-score $<$ -2.5 (indicating osteoporosis) (12) measured from the femoral neck using dual-energy X-ray absorptiometry (DXA), 2) resting knee pain visual analogue scale (VAS) $>$ 50/100, 3) a body mass index (BMI) of $>$ 34 kg/m² (due to confounding factors related to obesity in relation to original intervention), 4) surgery of the knee due to trauma or knee instability, 5) meniscectomy within the last 12 months, 6) inflammatory joint disease, 7) intra-articular steroid injections in the knee during the previous 12 months, 8) contraindications to MRI and 9) allergies to contrast agents or renal insufficiency. Additionally, in this study, all LTPA diaries needed to be returned from the follow-up period. In total 84 participants attended the 12-month post-intervention follow-up study.

Leisure-time physical activity diary

Each participant's LTPA (26) from the 12-month study period was recorded using a LTPA diary implemented in our previous studies (16, 23, 24). Participants marked their LTPAs each day for 12 months and were instructed only to mark activities that lasted at least 20 minutes at a time (i.e. duration, type and intensity). Duration was reported in minutes and was converted into hours. Metabolic equivalent task (MET-hours) per month was calculated by multiplying each marked activity by self-evaluated intensity (1 = Light, 2 = Moderate, 3 = Vigorous) according to Ainsworth et al. 2011 (1). Participants were divided into tertiles based on their average monthly METh for the 12-month period: lowest, middle and highest tertile (Table 1). Compliance for returning all diaries from the follow-up period was 97.4%. An example LTPA diary is provided in the supplemental digital content (see appendix A, Supplemental Digital Content 1, example Leisure-time physical activity diary from one follow-up month, <http://links.lww.com/MSS/A877>).

Primary outcome measures

Primary outcome measures for this study, T2 relaxation time (T2) mapping (milliseconds, ms) and the delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index, ms), were measured using a Siemens Magnetom Symphony Quantum 1.5-T scanner (Siemens AG, Medical Solutions, Erlangen, Germany). These methods provide information on the response of tibiofemoral cartilage to physiological loading (21, 28). T2 is a surrogate for the properties of the collagen network with lower values corresponding to better integrity and orientation of the collagen fibres and the hydration of the articular cartilage (18, 30). dGEMRIC index measures estimated GAG content of the knee articular cartilage with higher values

corresponding to higher estimated GAG concentration (2). The MRIs were performed by external radiographers and segmentation was performed blinded to original group allocation. Single sagittal slice images from the centre of the medial and lateral femoral condyles were taken from the affected knee with the highest K/L grade for both T2 and dGEMRIC index measurements. In cases of identical grading bilaterally, the right knee was imaged. Images were manually segmented using an in-house MATLAB application with built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). In this study, we divided the femoral cartilage into three ROIs: anterior, central and posterior. As illustrated in Figure 1, anterior and posterior borders of the anterior and posterior meniscus were used as landmarks to define the margins of the femoral and tibial cartilage ROIs. dGEMRIC indices were corrected for BMI (33). Precision, scan-rescan, (CV_{RMS}) of dGEMRIC in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage (22). In our laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was 1.3% to 3.3% and 2.8% to 4.0% for dGEMRIC. The full MRI protocol and example images are provided in the supplemental digital content (see appendix B, Supplemental Digital Content 2, MRI protocol and example of image segmentations, <http://links.lww.com/MSS/A878>).

Secondary outcomes

Physical performance

Cardiorespiratory fitness (VO_2 peak, ml/kg/min) was estimated using the UKK 2 km walking test (UKK Institute, Tampere, Finland) (19) and isometric knee extension and flexion force (N/kg) of the affected knee was measured at a 60 degree angle using an adjustable dynamometer chair

(Good strength; Metitur Ltd, Jyväskylä Finland) (29). Physical performance measurements have been described in detail in our study protocol (38).

Self-assessed impact of OA symptoms

Self-assessed impact of OA on pain, other symptoms, activities of daily living, sports and recreations and knee-related quality of life were assessed using the validated Finnish (15) Likert version of the knee injury and osteoarthritis outcome score (KOOS) questionnaire (27). Scores for each domain range from 0 to 100, with the score of 0 indicating extreme and 100 no knee problems.

Statistical analyses

The results are presented as means and standard deviations (SD). Statistical significance for the hypothesis of linearity between physical activity tertiles (lowest, middle and highest) with cartilage and physical performance traits were evaluated by using analysis of variance (ANOVA) and analysis of covariance (ANCOVA). T2 was adjusted for baseline value, height and weight. dGEMRIC index (already adjusted for BMI) and secondary outcomes were adjusted for baseline value only. The normality of the variables was tested by using the Shapiro-Wilk W test. Since two participants (2.6%) had missing LTPA diary data, last observation carried forward method was used. Statistical analyses were performed using statistical software (Stata, release 14.1, StataCorp, College Station, Texas).

RESULTS

During the 12-month follow-up, eight (10%) participants dropped out of the study. One participant died due to diagnosed cancer and one due to unknown reasons. In addition, one participant withdrew due to activated Ménière's disease, two due to personal reasons, one due to hip arthroplasty, one due to radiotherapy for breast cancer and one did not return the physical activity diaries from the entire follow-up period. Therefore, 76 (90%) participants completed the 12-month follow-up period. The division into METh tertiles was: 1=lowest (n=25), 2=middle (n=25) and 3=highest (n=26). Importantly, there was no difference between the LTPA METh tertiles according to the original intervention study groups (i.e. members of the training and control group) in the beginning or during the follow-up (Table 1).

Demographic and clinical characteristics of the study participants according to the LTPA (METh) in the beginning of the follow-up period (i.e. baseline) are shown in Table 2. At the baseline, there was a linear inverse relationship between body mass ($p<0.001$), BMI ($p<0.001$), cardiorespiratory fitness (VO_2 peak, $p<0.001$), muscle force (knee extension, $p<0.001$, knee flexion, $p=0.011$) and LTPA level. Most common LTPAs during the 12-month follow-up period were walking (including Nordic walking) (mean: 1h 5min/week, 1h 38min/week and 3h/week in the tertiles, respectively), and LTPA described as “other” (e.g. gardening and cleaning) (mean: 55min/week, 1h 13min/week and 1h 28min/week in the tertiles, respectively). Average monthly MET hours in LTPA tertiles for each follow-up month are provided in the supplemental digital content (see appendix C, Supplemental Digital Content 3, Average monthly MET hours in leisure time physical activity tertiles, <http://links.lww.com/MSS/A879>).

To ensure accuracy, each MRI image was inspected for quality, and exclusion required full agreement within the research group. All T2 data sets were included in the analysis. One complete dGEMRIC index data set was not measured due to participant's rejection of contrast agent injection. Additionally, from the dGEMRIC index, 21 participants had movement artifact in the medial condyle, while in the lateral condyle, 17 participants had either artery-flow pulsating artifact or movement artifact and one inaccurate location of the slice compared to baseline image. These data sets were therefore missing from the final analysis. In total 54 and 57 complete datasets for medial and lateral condyles respectively were available for quantitative dGEMRIC analysis.

T2 and dGEMRIC index change during the 12-month follow-up and p-value for linearity in relation to LTPA level are given in Table 3. In knee cartilage regions, there was a statistically significant linear relationship showing that dGEMRIC index in posterior ROI of the lateral ($p=0.003$) and medial ($p=0.006$) femoral cartilage increased with higher LTPA level during 12-month period. Furthermore, these changes were seen in the posterior lateral femoral cartilage superficial ($p=0.004$) and deep ($p=0.007$) ROIs and in the posterior medial superficial ROI ($p<0.001$) (Figure 2). No linear relationship was observed between LTPA level and changes in T2 relaxation time (Table 3), physical performance characteristics or self-assessed impact of OA symptoms (KOOS) during 12 months (Table 4).

DISCUSSION

To our knowledge, we are the first to demonstrate that long-term (12-month) LTPA level is related to regional increases in estimated GAG content of tibiofemoral cartilage in postmenopausal women with mild knee OA as measured with dGEMRIC index. This linear relationship was observed in the posterior region of medial and lateral femoral cartilage, which is less loaded during activities of daily living than the central region (37). Cardiorespiratory fitness, muscle force and all KOOS dimensions remained at the follow-up initiation level, and no linearity with LTPA tertiles was observed during 12 months.

Our results indicate that people with higher levels of LTPA during the 12-month follow-up period also had larger increases in the dGEMRIC index (i.e. estimated GAG content) within the cartilage of the posterior ROI of the medial and lateral femoral condyle. It has been suggested that in the dGEMRIC index, higher values correspond to higher knee articular cartilage GAG concentration (2). This can be interpreted to mean that when exposed to sufficient loading stimulus and environment, all chondrocytes, including cells extracted from OA cartilage, have a latent loading adaptation ability to regenerate and proliferate matrix (e.g. GAGs and collagen) (10, 31). Furthermore, our results are suggesting that persons with mild knee OA may have a lower threshold for chondrocyte adaptation in the posterior region of the femoral cartilage, which is less loaded during the activities of daily living compared to the central region. Our previous findings support this suggestion (24). Aforementioned results are also supported by several animal (3, 13, 14) and human studies in healthy population (31, 32, 34) and in people at a high risk of developing knee OA following surgery for meniscal injury (28), showing the beneficial

relationship between a physically active lifestyle and the maintenance of the biochemical properties of cartilage.

It has been suggested that GAG loss is an early feature in OA, and it occurs primarily in the superficial region of cartilage (4, 25), but the nature of responses and the exact region in osteoarthritic cartilage to exercise is not yet fully understood. In our present study, the dGEMRIC index (i.e. estimated GAG content) responded to LTPA similarly in the superficial and deep cartilage (i.e. full-thickness) in the posterior ROI of medial and lateral femoral cartilage. Our results are in line with the study by Hawezi *et al.* (9), who also showed that a change in the dGEMRIC index due to a change in the physical activity level occurred both in the superficial and deep cartilage regions (i.e. full-thickness) in people with a risk of developing OA. However, this full-thickness effect may be at least partly explained by the relatively large decrease in the dGEMRIC index seen in the deep ROI of the posterior condyle. Additionally, the diffusion of the contrast agent is influenced by the cartilage thickness, where thinner cartilage results in a lower dGEMRIC index (8). In our study, cartilage thickness was not measured, leaving this issue open to speculation and for further investigation.

In our study, no linear relationship was observed between a 12-month period of LTPA and changes in T2 relaxation time. T2 measures different cartilage attributes than dGEMRIC index, indicating that a low T2 value corresponds to better integrity and orientation of the collagen fibres and a decrease in the hydration of the articular cartilage (18, 30). In our previous exercise intervention study we found that a 4-month progressive aquatic resistance training program (i.e. full range of motion with high repetition low shear and compressive cyclic forces) improved the

estimated biochemical composition of the medial posterior tibiofemoral cartilage as measured with T2 (24). The benefit of this type of loading pattern for integrity and orientation of the collagen fibres is also supported by our previous land-based RCTs (16, 23). Koli *et al.* (16) showed that a 12-month progressively implemented high-impact and intensive jumping exercise (i.e. impact exercises were shear with moderate compression in the patellofemoral joint) in postmenopausal women with mild knee OA improved the estimated biochemical composition of the patellar cartilage as measured with T2. Using the same intensive intervention, Multanen *et al.* (23) showed that no positive or negative effect was observed in the biochemical composition of tibiofemoral cartilage (i.e. T2 or dGEMRIC index). The LTPAs may not have exposed the knee joint to optimal and sufficient intensity and loading to cause adaptation in the integrity of the collagen-interstitial water environment (T2) in the tibiofemoral cartilage. However, GAG concentration (i.e. dGEMRIC index) may be more responsive to intermittent impact and compression type of loading in people with mild tibiofemoral knee OA and may therefore partly explain the findings of this study. This explanation is also supported by Roos and Dahlberg 2005 (28). More controlled (type of exercise, loading, frequency, duration and intensity) exercise interventions are needed in order to determine the most optimal loading and intensity for improving overall cartilage quality in osteoarthritic population.

In this study, walking (including Nordic walking) accounted for 40% of the total LTPA.

Gait on level surface requires knee range of motion from nearly full extension to 60-65 degree flexion (37), and knee flexion of over 90 degrees is required to produce contact between posterior ROI of femur and central tibia (7). Therefore, the biomechanics of gait do not solely explain why an increase in dGEMRIC index was observed in the posterior ROIs of cartilage. The

average peak knee joint loading during normal gait is in the range of 2 to 4.5 times body weight (17, 40). Thus, it can be speculated that the effects of intermittent impact and compressive loading during gait to knee central cartilage might have had favorable adjacent effects on less customary loaded posterior cartilage (e.g. trough pressure changes and muscle contraction) with a higher LTPA level. This higher repetitive mechanical stimulus might have been sufficient to cause beneficial changes, such as improved fluid flow and nutrient diffusion in the posterior ROI of the femoral cartilage. On the other hand, repetitive knee bending exposure (i.e. deep knee bending or kneeling for 30 minutes or more) has been associated with an increased risk of prevalent cartilage lesion especially in patellofemoral compartment in males and females between the ages 45 and 55 with a risk for OA (35). In our study, the activity described as “other” (e.g. gardening and cleaning) accounted for 23% of the total LTPA. These activities might have included non-repetitive uncusomary loading to the knee (i.e. higher knee flexion with larger range of motion), which can be hypothesised to have caused beneficial changes in less loaded posterior ROI of femoral cartilage. In our previous study (24) we discussed that the chondrocytes in the posterior region of the femoral cartilage in persons with mild knee OA may have a lower threshold for adaption compared to the central region, and in contrast, the chondrocytes in the central region of the femur and tibia cartilage may require a higher or atypical loading compared to customary loading in order to stimulate an adaptive response. Thus, posterior less customary loaded medial and lateral femoral condyle cartilage might be more responsive to light exercise than the central cartilage. Therefore, even light LTPA performed regularly in the long-term may be sufficient enough to positively stimulate the less customary loaded posterior region of medial and lateral femoral cartilage, which was observed in our study

as increased estimated GAG concentration. Also, LTPA even at the highest level was well tolerated and did not increase clinical symptoms in women with mild knee OA.

The strengths of this study include the long-term follow-up period (12-months) and high adherence to the end measurements with no harms observed as LTPA level increased. In addition, each participant's daily physical activity was monitored each day throughout the whole 12-month follow-up period. Strict imaging procedure and segmentation rules ensured good stability and repeatability of the T2 relaxation time and dGEMRIC indices. This limits the possible effects of the magic angle (particularly T2) and partial volume effects. The long imaging time in dGEMRIC mapping might result in motion artefact, which was controlled for in our study by using a motion correction technique built into the in-house software as well as a strict inclusion/exclusion criterion for image quality (i.e. excessive movement and pulsating artefact). This study also had some minor limitations, which were related to the MRI imaging and analysis technique. We used a 1.5 tesla scanner, whereas a 3.0 tesla scanner would have produced better spatial resolution and a higher signal-to-noise ratio. In some cases occasionally thinned and deteriorated cartilage and movement (despite the motion correction technique) or pulsating artery artefact prevented reliable segmentation of cartilage resulting in lost data. Also, the single-slice segmentation method utilised in this study assesses only a restricted region of the cartilage, whereas the multi-slice method might have produced a more comprehensive representation of the tibiofemoral cartilage. The segmentation software automatically divided cartilage of each full-thickness ROI into deep and superficial compartments (50%/50%). However, due to the 1.5T scanner used, segmented cartilage thickness ranged from two to five voxels, thus reducing the spatial accuracy. Due to the strict inclusion criteria in the original

intervention study (24), our results cannot be directly applied to people with later stage OA or older or extremely obese women and men. Finally, the authors acknowledge that so far there is no “golden standard” method to measure how exercise directly affects the biochemical composition of cartilage in vivo. Therefore, the different qMRI parameters and their interactions are not yet fully understood (2) and further investigations about the interaction between exercise, cartilage and these parameters are needed.

In conclusion, these results suggest that higher LTPA level is related to regional increases in estimated GAG content of tibiofemoral cartilage as measured with dGEMRIC index during a 12-month period. These results have an important role when assessing physical activity levels for cartilage quality related exercise intervention studies and also in clinical rehabilitation in postmenopausal women with mild tibiofemoral knee OA.

Acknowledgements

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FIGURE LEGENDS:

Figure 1. Illustration of the region of interests (ROIs) in the full-thickness femoral and tibial cartilage. Midlines split both femoral and tibial cartilage into superficial and deep sections. ROIs were segmented according to the landmarks as follows for central femoral cartilage: from the anterior end of anterior meniscus (arrow 1) to the posterior end of the posterior meniscus (arrow 2) and for central tibial cartilage: from the posterior end of anterior meniscus (arrow 3) to the anterior end of the posterior meniscus (arrow 4).

Figure 2. dGEMRIC index change during the 12-month follow-up from femoral posterior lateral and medial superficial and deep ROIs according to LTPA (Metabolic Equivalent hour, MET_h) tertiles.

SUPPLEMENTAL DIGITAL CONTENT:

Appendix A.docx—An example Leisure-time physical activity diary from one follow-up month

Appendix B.docx—MRI protocol and example of image segmentations

Appendix C.docx—Average monthly MET hours in leisure time physical activity tertiles

Figure 1

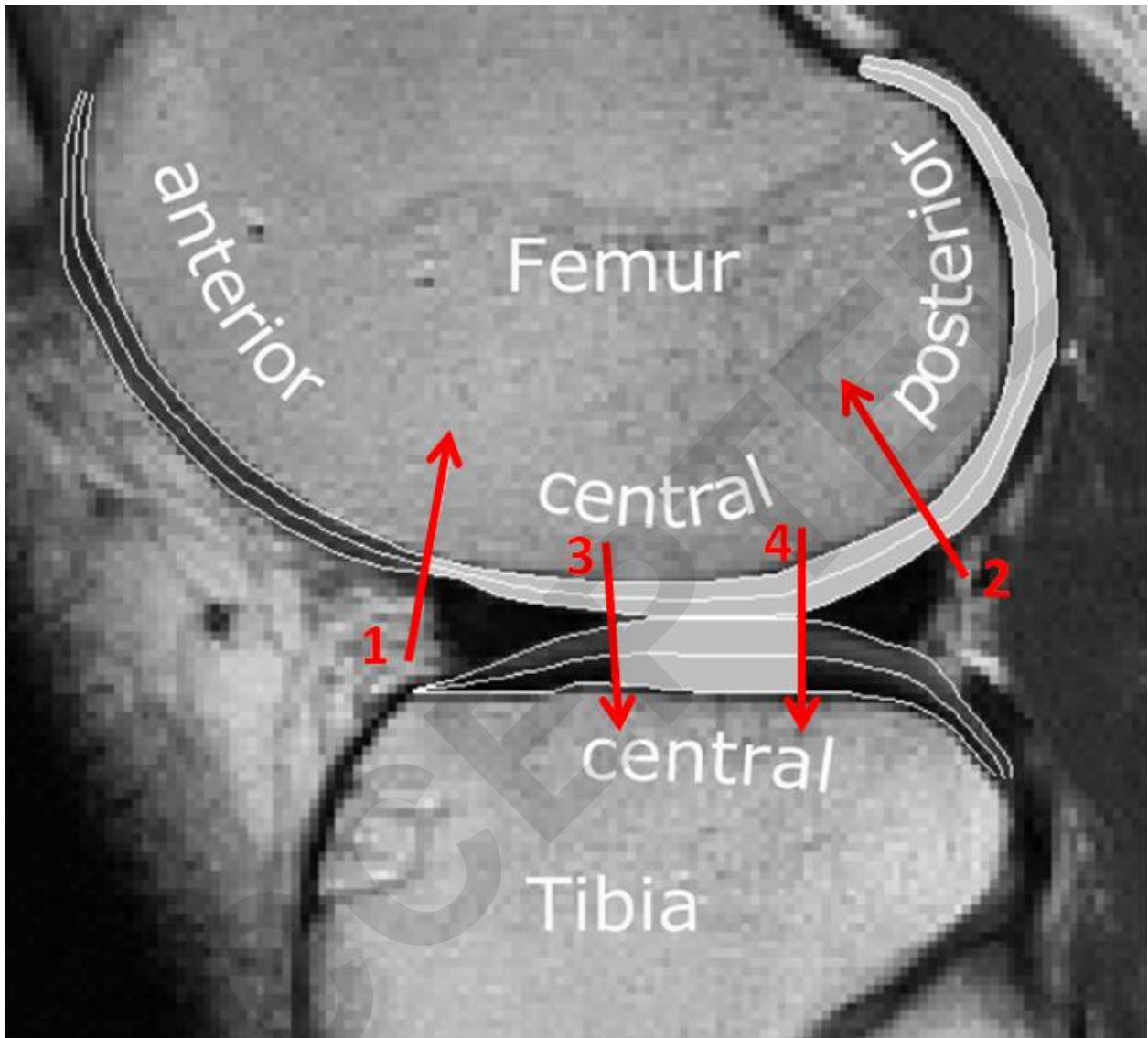


Figure 2

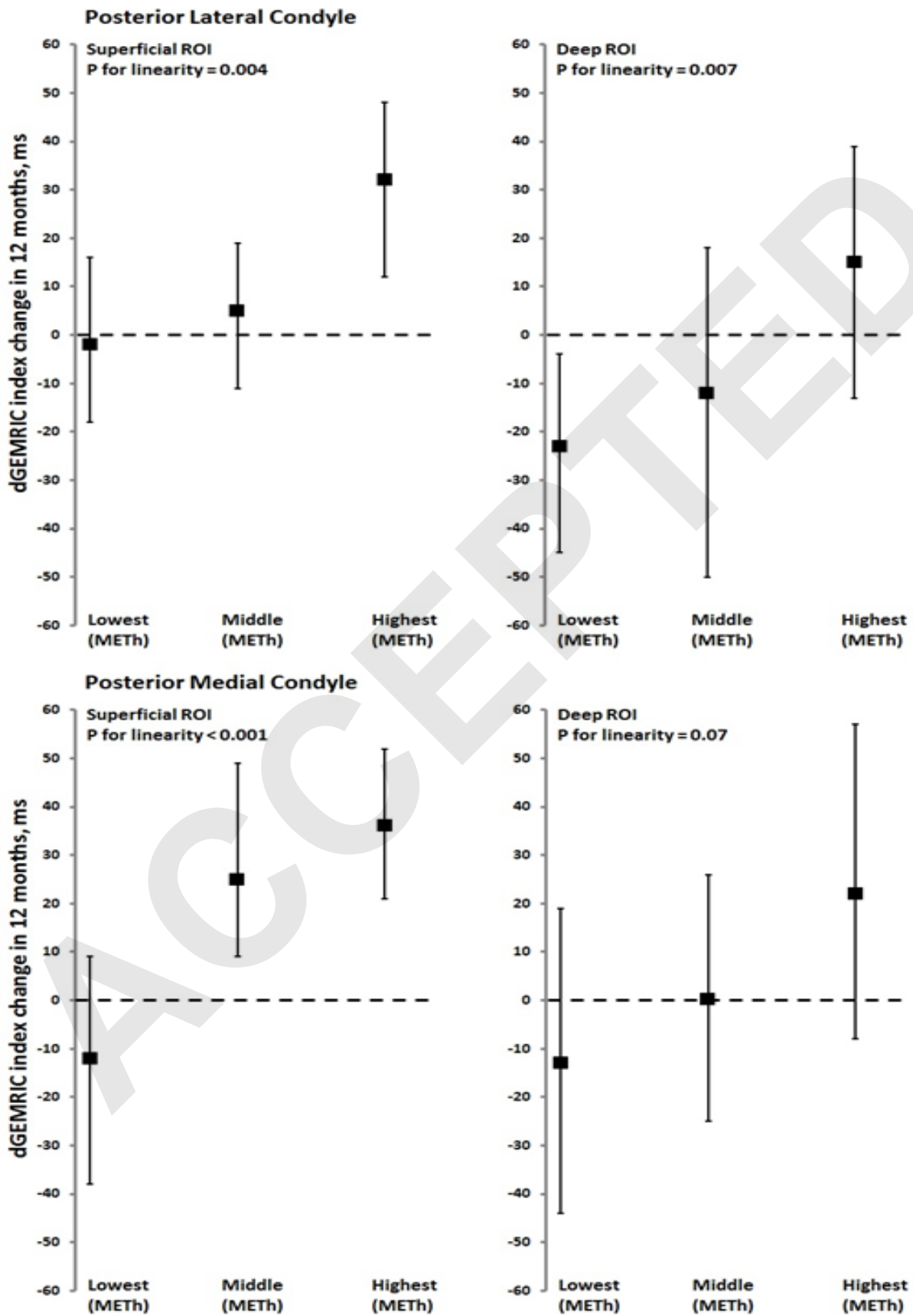


Table 1. Average monthly METh for the follow-up period.

	Lowest METh (n=25)	Middle METh (n=25)	Highest METh (n=26)
All participants			
METh, mean (SD)	52 (15)	97 (14)	155 (29)
Original intervention group			
Number (%)	16 (64.0)	12 (48.0)	11 (42.3)
METh, mean (SD)	53 (15)	96 (14)	156 (36)
Original control group			
Number (%)	9 (36.0)	13 (52.0)	15 (57.7)
METh, mean (SD)	49 (15)	98 (15)	155 (26)

Original intervention group: Intervention group of the original RCT design. Original control group: Control group of the original RCT design.

Table 2. Demographic and clinical characteristics of the participants at the beginning of 12-month follow-up.

	Lowest METH (n=25)	Middle METH (n=25)	Highest METH (n=26)	P for linearity
Age (years)	64 (2)	64 (3)	65 (2)	0.39
Height (cm)	162 (5)	161 (5)	163 (4)	0.47
Body mass (kg)	76.4 (10.8)	69.1 (10.8)	65.3 (9.1)	<0.001
Body mass index (kg/m ²)	28.9 (3.4)	26.6 (3.8)	24.5 (3.0)	<0.001
Cartilage traits				
T2, (ms) Femur				
Lateral condyle: Central	52.1 (4.8)	51.8 (3.3)	54.7 (4.4)	0.053
Lateral condyle: Posterior	48.5 (4.3)	49.8 (3.7)	50.0 (3.3)	0.16
Medial condyle: Central	51.8 (6.6)	53.7 (3.6)	51.8 (5.1)	0.99
Medial condyle: Posterior	51.0 (4.3)	52.1 (3.5)	51.0 (5.4)	0.99
T2, (ms) Tibia				
Lateral plateau: Central	42.4 (9.1)	41.0 (6.8)	41.9 (9.2)	0.85
Medial plateau: Central	43.5 (5.3)	44.3 (3.8)	43.1 (4.8)	0.76
dGEMRIC index, (ms) Femur				
Lateral condyle: Central	419 (56)	425 (64)	433 (48)	0.70
Lateral condyle: Posterior	424 (66)	427 (85)	428 (54)	0.85
Medial condyle: Central	398 (53)	392 (77)	423 (44)	0.13

Medial condyle: Posterior	434 (66)	447 (68)	449 (63)	0.60
dGEMRIC index, (ms) Tibia				
Lateral plateau: Central	394 (83)	442 (94)	418 (79)	0.17
Medial plateau: Central	373 (61)	374 (73)	380 (48)	0.92

Physical performance

Cardiorespiratory fitness, (ml/kg/min)

Estimated VO ₂ peak	24.6 (3.9)	26.8 (5.9)	29.5 (4.1)	<0.001
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Muscle Force, (N/kg)

Knee extension	4.4 (0.8)	5.6 (1.2)	5.7 (1.4)	<0.001
Knee flexion	2.4 (0.5)	2.8 (0.7)	2.9 (0.9)	0.011

Clinical symptoms

KOOS, range 0-100mm

Pain	83 (11)	85 (11)	85 (11)	0.70
Other symptoms	80 (12)	80 (13)	81 (13)	0.72
ADL	86 (12)	88 (14)	88 (10)	0.66
Sport	67 (24)	69 (30)	73 (17)	0.33
QOL	72 (20)	76 (22)	76 (18)	0.50

Values are means (SD)

METH = metabolic equivalent task hour (Tertiles based on participants average monthly METH)

T2 = transverse relaxation time = high values correspond to compromised cartilage structure degeneration. dGEMRIC index = high values correspond to high glycosaminoglycan concentration.

KOOS = Knee Injury and Osteoarthritis Outcome Score, ADL= activities of daily living, Sport = sports and recreation, QOL = knee related quality of life

Table 3. Cartilage trait value change during 12-month follow-up from different anatomical regions according to Metabolic Equivalent (MET) values.

	Change to month 12, mean (95% CI)		
	Lowest METh	Middle METh	Highest METh
	(n=25)	(n=25)	(n=26)
T2, ms			
Femur			
Lateral condyle			
Central	0.29 (-1.23 to 1.54)	0.62 (-0.58 to 1.89)	-0.62 (-2.07 to 0.45)
Posterior	-0.97 (-2.17 to -0.003)*	-1.29 (-2.47 to 0.002)	-0.87 (-2.20 to 0.32)
Medial condyle			
Central	-0.25 (-1.66 to 1.15)	-1.00 (-2.04 to -0.07)*	-0.13 (-1.57 to 1.22)
Posterior	0.14 (-0.81 to 1.16)	-0.81 (-1.76 to 0.17)	0.05 (-0.86 to 0.95)
Tibia			
Lateral plateau			
Central	-1.24 (-3.40 to 0.72)	-0.77 (-2.50 to 0.87)	-0.25 (-1.96 to 1.30)

Medial plateau			
Central	-0.86 (-2.32 to 0.55)	-0.15 (-1.56 to 1.09)	-0.68 (-2.26 to 0.81)
dGEMRIC index[†], ms			
Femur			
Lateral condyle⁺			
Central	-8 (-22 to 5)	-14 (-31 to 4)	8 (-14 to 27)
Posterior	-17 (-32 to -2)*	-8 (-35 to 12)	18 (-5 to 37)
Medial condyle[§]			
Central	-7 (-23 to 10)	12 (-7 to 27)	9 (-5 to 24)
Posterior	-17 (-39 to 6)	5 (-12 to 24)	24 (2 to 49)*
Tibia			
Lateral plateau			
Central	-8 (-24 to 9)	-22 (-44 to 1)	2 (-15 to 21)
Medial plateau			
Central	-17 (-34 to 4)	-13 (-42 to 11)	2 (-17 to 20)

T2 = transverse relaxation time; ^a adjusted for baseline value, height and weight.

dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ^b adjusted for baseline value.

In T2 low values correspond to improved integrity and orientation of the collagen fibres and a decrease in hydration of articular

In dGEMRIC index, high values correspond to high glycosaminoglycan concentration.

[†]Missing data for dGEMRIC ⁺n=18, [§]n=22

* Within-group change was statistically significant at $p < 0.05$ level

Table 4. Physical performance and clinical symptoms change to month 12 according to Metabolic Equivalent (METh) values.

	Change to month 12, mean (95% CI)		
	Lowest METh (n=25)	Middle METh (n=25)	Highest METh (n=26)
Cardiorespiratory fitness (ml/kg/min)			
Estimated VO ₂ peak	-1.0 (-2.6 to 0.6)	-0.5 (-1.8 to 0.7)	-0.7 (-1.6 to 0.1)
Muscle force (N/kg)			
Knee extension	-0.1 (-0.3 to 0.1)	0.0 (-0.3 to 0.3)	0.0 (-0.3 to 0.2)
Knee flexion	-0.1 (-0.2 to 0.1)	0.0 (-0.2 to 0.1)	0.0 (-0.2 to 0.1)
KOOS (0-100)			
Pain	-0.8 (-5.1 to 3.5)	-2.4 (-5.2 to 0.3)	-1.5 (-6.9 to 3.9)
Other symptoms	1.0 (-3.2 to 5.2)	0.0 (-2.3 to 2.3)	0.4 (-3.2 to 4.1)
ADL	-1.00 (-4.7 to 2.7)	-1.4 (-6.0 to 3.2)	-1.9 (-4.8 to 0.9)
Sport	1.0 (-7.2 to 9.2)	2.4 (-4.2 to 9.0)	-2.7 (-9.9 to 4.6)
QOL	-1.0 (-7.9 to 5.9)	1.3 (-3.2 to 5.7)	-5.0 (-12.5 to 2.4)

KOOS = Knee injury and osteoarthritis outcome score, ADL= activities of daily living; Sport = sports and recreation; QOL = knee related quality of life

^aAdjusted for baseline

Appendix A: An example Leisure-time physical activity diary from one follow-up month

Leisure time physical activity: June 2013 (Follow-up)

Name: _____

Randomisation number: _____

Study ID: __/__/__/__/__/__/__/__

Mark into the leisure time physical activity diary all activities that you have **performed each day (at least 20 minutes at time)**. Mark also **how long the physical activity lasted (in minutes)** and how **exhausting** (light = *, moderate = **, Vigorous = ***) your activity was.

- * Light = no sweating, no heavy breathing
- ** Moderate = somewhat sweating or increased breathing
- *** Vigorous = heavy sweating or heavy breathing

Leisure time physical activity	Leisure time physical activity
1. Jogging or running	11. Home gymnastics
2. Orienteering	12. Supervised aerobic
3. Cross-country skiing	13. Dance in different forms
4. Bicycling	14. Water aerobics
5. Walking	15. Stretching
6. Nordic walking	16. Yoga/ Tai-Chi
7. Golf	17. Badminton
8. Swimming	18. Tennis
9. Rowing/canoeing	19. Downhill skiing
10. Gym/Circuit training	20. Horse riding
	21. Something else, what? _____

June 2013. Mark **activities** by using number code from the list in previous page, **duration in minutes** (at least 20 minutes) and **exhaustion**.

WK	Monday	Tuesday	Wednesday	Thursday	Friday		
22	/	/	/	/	EXAMPLE! Activity: <u>5</u> Duration: <u>60</u> Intensity: <u>***</u>	Activity Duration Intensity _____ _____	
23	3	4	5	6	7	Activity: _____ Duration: _____ Intensity: _____ _____ _____	Activity Duration Intensity _____ _____
24	10	11	12	13	14	Activity: _____ Duration: _____ Intensity: _____ _____ _____	Activity Duration Intensity _____ _____
25	17	18	19	20	21	Activity: _____ Duration: _____ Intensity: _____ _____ _____	Activity Duration Intensity _____ _____

26	<p style="text-align: right;">24</p> Activity: _____ Duration: _____ Intensity: _____ _____ _____	<p style="text-align: right;">25</p> Activity: _____ Duration: _____ Intensity: _____ _____ _____	<p style="text-align: right;">26</p> Activity: _____ Duration: _____ Intensity: _____ _____ _____	<p style="text-align: right;">27</p> Activity: _____ Duration: _____ Intensity: _____ _____ _____	<p style="text-align: right;">28</p> Activity: _____ Duration: _____ Intensity: _____ _____ _____	Activity Duration Intensity _____ _____
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ACCEPTED

Appendix B: MRI protocol and example of image segmentations

Prior to MRI imaging, the participant was advised to restrain from any strenuous physical activity during the 48 hours prior to the measurements to minimize possible transient changes in knee cartilage volume and composition. Participants were imaged at the same time of the day to avoid possible diurnal variation at the follow-up measurements.

The participants were imaged lying supine. The knee was positioned into the coil by adjusting inferior margin of patella according to the centre of line of the coil. The flexion angle and rotation of the knee was controlled by stabilising the ankle to a fixed position within the knee coil by using a leg holder and a custom made inflatable cushion. The cushion was specifically designed to stabilize the patella without causing any compression of the patellofemoral joint. The imaging session lasted 3 hours and included a standard clinical MRI series and T2 relaxation time followed by the dGEMRIC series.

T2 mapping was performed using a sagittal multi-slice multi-echo fast spin echo sequence (field of view (FOV) 140mm, acquisition matrix 256 x 256, repetition time (TR) 2090 ms, eight echo times (TE) between 13 and 104 ms, echo train length (ETL) 8, slice thickness 3 mm). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. Two slices, each covering the central region of the medial and lateral condyles, were analysed.

For the dGEMRIC series, immediately after the clinical and T2 imaging, an intravenous injection of 0.4mL/kg (double dose) of Gd-DTPA²⁻ (Magnevist, Schering, Berlin) was administered. The amount of contrast agent administered was corrected for body weight at

each measurement point. This was appropriate because of the expected changes in body composition as a result of the intensive exercise intervention. In order to enhance the delivery of contrast agent into the knee cartilage, following administration of Gd-DTPA²⁻, the participants were instructed to perform 5 minutes of knee flexion-extension exercises in a sitting position without resistance, 5 minutes of walking on a flat surface and 10 gentle deep squats. Exactly ninety minutes after the injection, dGEMRIC mapping in the presence of Gd-DTPA²⁻ was performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV = 14 cm, matrix 256 x 256, TR = 1800 ms, TE 13 ms, six inversion times (TI) between 50 and 1600 ms, slice thickness 3 mm). The slice positioning was copied from the T2 relaxation time mapping sequence, and the number of the slice in the correct orientation is reduced to one. The remaining slice was then positioned at the centre of the medial and lateral condyles as viewed on the axial scout image. The participants were positioned into an identical position as for the first MRI imaging. Knee with highest degree of OA, as measured by the radiographic Kellgren-Lawrence (K/L) scale, was imaged. In the cases where both knee had identical K/L score the right knee was imaged.

For quality assurance purposes, a set of phantom samples containing certain concentrations of agarose and nickel nitrate to modulate their dGEMRIC and T2 relaxation times were imaged following the study protocol prior to baseline and follow-up measurement sessions, and no evidence of scanner drift was observed during the intervention.

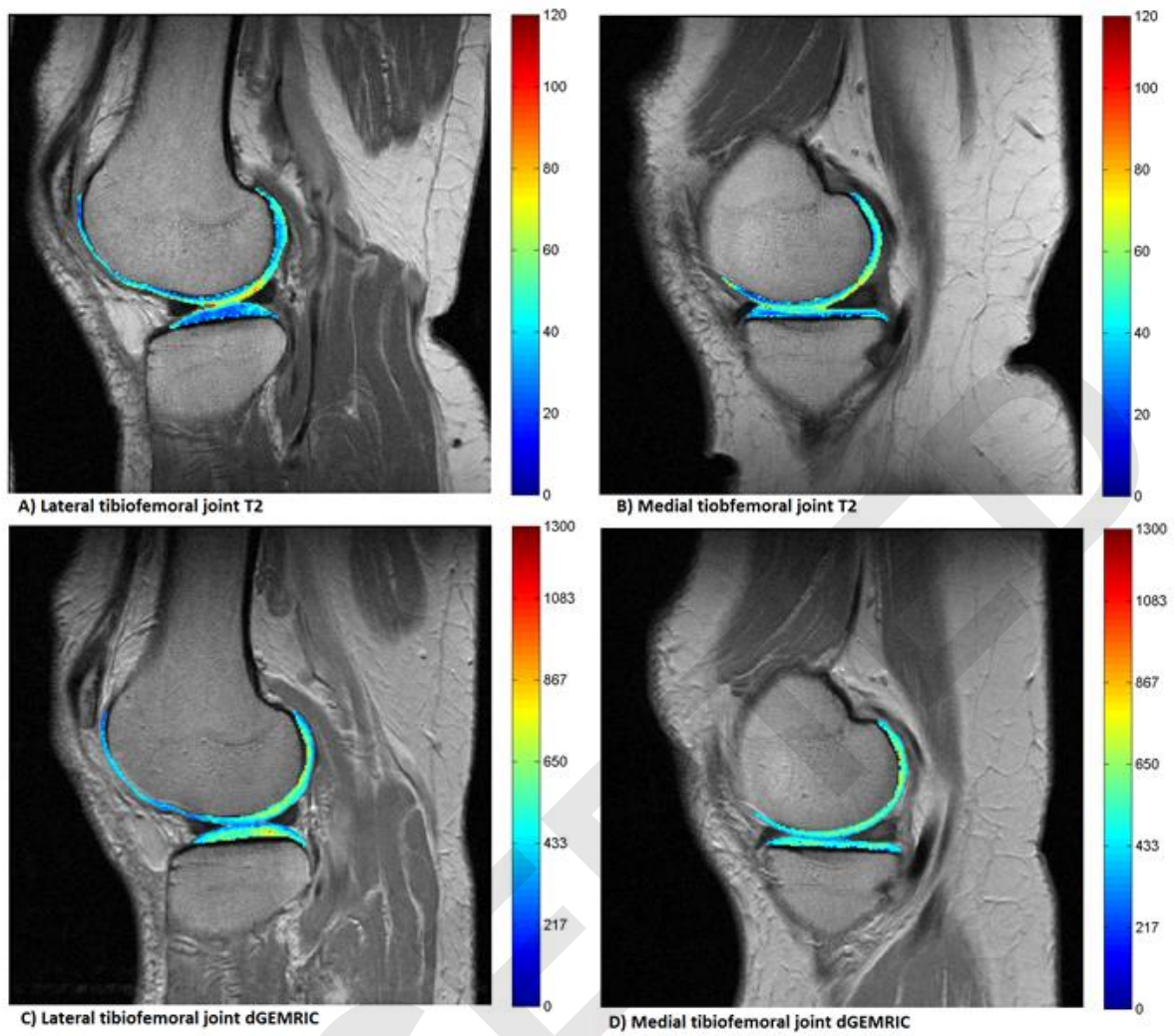


Figure 1. Example image of T2 and dGEMRIC segmentation

Appendix C: Average monthly MET hours in leisure time physical activity tertiles

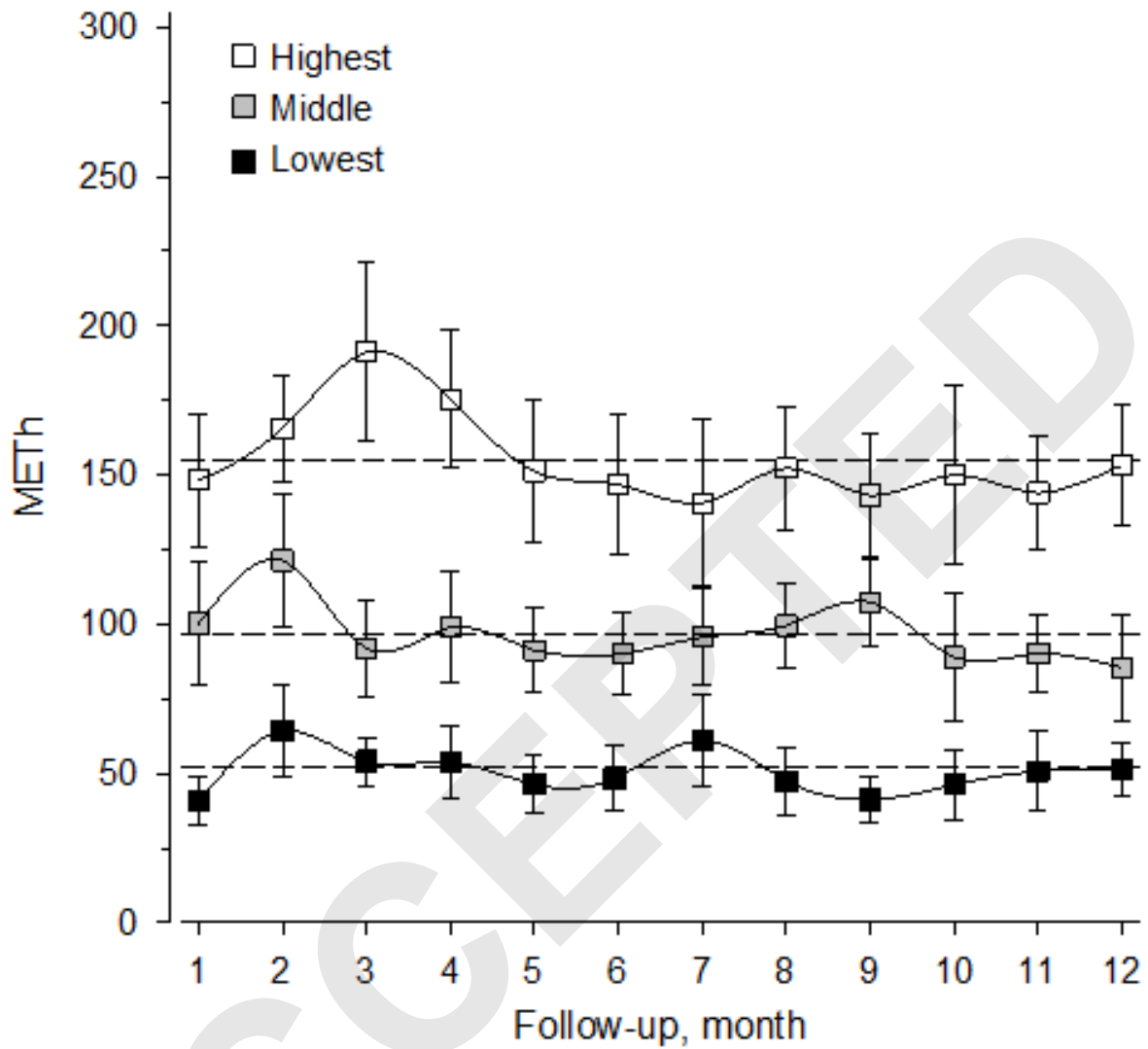


Figure 1. Average monthly MET hours in leisure time physical activity tertiles