Title

Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative

Journal

Osteoarthritis and Cartilage, 21(10)

ISSN

1063-4584

Authors

Lin, W
Alizai, H
Joseph, GB
et al.

Publication Date

2013-10-01

DOI

10.1016/j.joca.2013.06.022

Peer reviewed

Published in final edited form as:
Osteoarthritis Cartilage. 2013 October ; 21(10): . doi:10.1016/j.joca.2013.06.022.

Physical activity in relation to knee cartilage T2 progression measured with 3 T MRI over a period of 4 years: data from the Osteoarthritis Initiative

W. Lin[†], **H. Alizai**[†], **G.B. Joseph**[†], **W. Srikhum**[†], **M.C. Nevitt**[‡], **J.A. Lynch**[‡], **C.E. McCulloch**[‡], and **T.M. Link**[*,†]

[†] Musculoskeletal and Quantitative Imaging Research, Department of Radiology and Biomedical Imaging, University of California San Francisco, 185 Berry Street, Suite 350, San Francisco, CA 94107, USA

[‡] Department of Epidemiology and Biostatistics, University of California San Francisco, 185 Berry Street, Suite 5700, San Francisco, CA 94107, USA

SUMMARY

Objective—The purpose of this study was to analyze the longitudinal association between physical activity levels and early degenerative cartilage changes in the knee, measured using T2 relaxation times over a period of 4 years in individuals without clinical or radiographic evidence of OA.

Design—Cartilage T2 was measured at baseline and after 2 and 4 years in 205 subjects aged 45–60 years from the Osteoarthritis Initiative (OAI) incidence and normal cohorts with no knee pain (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score of zero), and a Kellgren Lawrence (KL) score of <2 at baseline. Physical activity was scored using the Physical Activity Scale for the Elderly (PASE) questionnaire, which was obtained yearly over 4 years. The relationship between physical activity and T2 was studied using a mixed model linear regression, including random effects, and adjusted for age, sex, and body mass index (BMI).

Results—T2 values for all PASE tertiles progressed over the 4-year period. T2 progression was increased in the highest tertile of physical activity compared to the mid-tertile at the medial tibia (MT) ($P = 0.041$), patella (Pat) ($P = 0.019$), and average T2 of all knee compartments combined ($P = 0.033$). Subjects with the lowest 15% PASE scores showed significantly higher T2 progression compared to the mid-level physical activity group at the lateral femur (LF) ($P = 0.025$), lateral tibia (LT) ($P = 0.043$), medial femur (MF) ($P = 0.044$), tibiofemoral compartment

[*] Address correspondence and reprint requests to: T.M. Link, Department of Radiology and Biomedical Imaging, UCSF, 400 Parnassus Ave, A-367, Box 0628, San Francisco, CA 94143, USA. tmlink@radiology.ucsf.edu (T.M. Link).. wilson.lin@ucsf.edu (W. Lin), hamza.alizai@ucsf.edu (H. Alizai), gabby.joseph@ucsf.edu (G.B. Joseph), waraporn.srikhum@ucsf.edu (W. Srikhum), mnevitt@psg.ucsf.edu (M.C. Nevitt), jlynch@psg.ucsf.edu (J.A. Lynch), cmcculloch@epi.ucsf.edu (C.E. McCulloch), thomas.link@ucsf.edu

Author contributions

Wilson Lin is the primary author and contributed to the manuscript in the following ways: conception and design, data segmentation, analysis and interpretation of data, statistical modeling, manuscript drafting and revision. The following authors contributed as described: Hamza Alizai (conception and design, segmentation, analysis and interpretation of data, manuscript revision), Gabby Joseph (statistical expertise, data analysis, manuscript revision), Waraporn Srikhum (data acquisition and analysis, manuscript revision), Michael Nevitt (conception and design, manuscript revision), John Lynch (conception and design, manuscript revision), Charles McCulloch (conception and design, statistical expertise, manuscript revision), and Thomas Link (study supervisor, conception and design, data analysis and interpretation, manuscript drafting and revision).

Conflicts of interest

None of the authors of this study have any conflicts of interest in this study.

($P = 0.017$), patellofemoral compartment ($P = 0.016$), lateral compartments ($P = 0.003$), and average of all compartments ($P = 0.043$).

Conclusion—High and very low PASE scores were associated with greater progression of cartilage T2 measurements in asymptomatic, middle-aged individuals, suggesting accelerated cartilage matrix biochemical degeneration over time.

Keywords

Physical activity; MRI; T2 relaxation time; Cartilage; Knee

Introduction

While many known risk factors for OA have been identified, the relationship between physical activity and OA onset is unclear and complex[1–3]. Some studies suggest that exercise may cause or accelerate OA[4,5], while others promote exercise as a mode of prevention and treatment[6–8]. In these studies, outcomes were measured in terms of radiographs or clinical symptoms. Given the gradual and progressive nature of OA, the examination of physical activity in relation to biochemical changes in cartilage may enhance our understanding of the role that physical activity plays in this disease.

Magnetic resonance imaging (MRI) is a noninvasive imaging technique that has become more commonly used for visualizing morphologic abnormalities in knee OA. However, by the time morphological changes are visualized, irreversible loss of cartilage has already occurred. MRI techniques to assess early biochemical changes in the cartilage matrix have been developed and include T2 relaxation time mapping, a technique sensitive to changes in water content and collagen integrity[9]. Studies have demonstrated an association between severity of OA lesions and prolonged T2 relaxation times[10,11]. T2 mapping would therefore be a suitable method to analyze the gradual effects of physical activity on cartilage health[12].

Few studies have investigated the relationship between physical activity and T2 values. Higher levels of physical activity have been found to be associated with higher T2 measurements, suggesting greater cartilage degeneration in these individuals[13,14]. However, these studies were cross-sectional. There is a scarcity of data analyzing the effects of physical activity in relation to longitudinal changes in T2 measurements.

The purpose of our study was therefore to assess the longitudinal association between physical activity levels acquired using the Physical Activity Scale for the Elderly (PASE) questionnaire and cartilage degeneration using T2 relaxation time over a 4-year period in middle-aged asymptomatic subjects with and without risk factors for OA. Our study used data from the Osteoarthritis Initiative (OAI), a multi-center longitudinal cohort study that is sponsored by the National Institutes of Health[15].

Materials and methods

Subjects

The OAI is a large-scale multi-center longitudinal cohort study of OA and includes MRI-based imaging biomarkers and their role in the progression of knee OA. The study consists of 4796 individuals from four recruitment sites, either with or at risk of developing osteoarthritis, in addition to a smaller number of normal, healthy controls[15]. The OAI provides baseline and longitudinal data including annual MR images of subjects over a period of 4 years, which are publicly available at http://www.oai.ucsf.edu/. The study

protocol, amendments, and informed consent documentation including analysis plans were reviewed and approved by local institutional review boards.

A subset of 205 subjects without symptomatic or radiographic evidence of OA (Kellgren Lawrence (KL) score ≤1) was included from the incidence (no OA but presence of OA risk factors) and normal (no OA and no OA risk factors) cohorts of the OAI. The specific OA risk factors included knee pain, obesity, prior knee injury, prior knee surgery, family history of knee replacement, Heberden's nodes, and frequent knee-bending activity. The specific inclusion criteria for the presented study were age 45–60, body mass index (BMI) of 19–27 kg/m^2, no knee pain in either knee (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[16] pain score of zero in both knees at baseline), and a Kellgren Lawrence (KL) score ≤1 in right knee radiographs at baseline. Exclusion criteria included severe joint space narrowing, rheumatoid arthritis, MRI contraindications, and an incomplete data set from the OAI database. These specific inclusion criteria were used to identify patients in the early stage of the OA disease process, when cartilage matrix imaging biomarkers would be most advantageous for measuring subtle disease progression. Forty normal cohort subjects and 165 incidence cohort subjects fulfilled the inclusion and exclusion criteria (Fig. 1). Since the normal cohort alone would not have garnered sufficient power, subjects from the normal cohort and incidence cohort were analyzed together.

Imaging

Radiographs—A plexiglass frame (SynaFlexer) was used to obtain bilateral standing posteroanterior fixed flexion knee radiographs. Knees were placed in 20–30° flexion and the feet were placed with 10° internal rotation. A focus-to-film distance of 72 inches was used. Two radiologists, in consensus, evaluated and graded the radiographs using the K/L scale[17].

MR imaging protocol—MR images were obtained using four identical 3.0 T (Siemens Magnetom Trio, Erlangen, Germany) scanners and quadrature transmit-receive coils (USA Instruments, Aurora, OH, USA) at four sites (The Ohio State University, Columbus, OH; University of Maryland, School of Medicine, Baltimore, MD; University of Pittsburgh, Pittsburgh, PA; and Memorial Hospital of Rhode Island, Pawtucket, RI). A sagittal T2 map 2-D Multi-Slice Multi-Echo (MSME) spin-echo sequence (TR/TE = 2700/10,20,30,40,50,60,70 ms (milliseconds), spatial resolution = 0.313 mm × 0.446 mm, slice thickness = 3 mm) was used for the measuring T2 relaxation times; the exact protocol details have been published previously[18,19]. Rigorous quality assurance was performed including phantom measurements at all four sites. Over 8 years, testeretest reproducibility of T2 relaxation time values were 2.1%–5.5% root mean square (RMS) coefficient of variation (CV%) in phantom studies[20,21].

Image analysis – quantitative T2 relaxation time measurements—Sagittal 2-D Multiecho spin-echo images of the right knee were transferred to a remote workstation for offline quantification of T2 relaxation time using an in-house developed spline-based, semi-automated software (automated edge detection and manual correction) segmentation algorithm in MATLAB (Mathworks Inc, El Segundo, CA)[22,23]. Segmentation of the cartilage was performed on the first echo sequence for maximum signal-to-noise ratio. The following compartments were segmented in entirety on all slices with well-visualized artifact-free cartilage: patella (Pat), medial femoral condyle (MFC), lateral femoral condyle (LFC), medial tibia (MT), and lateral tibia (LT). Due to interfering flow artifacts from the popliteal artery, the trochlea was not segmented. The segmentation process was performed on images from baseline, 24-month follow-up, and 48-month follow-up for each patient. We used the interactive display language routine to calculate the mean T2 value for each region of interest. The T2 relaxation time was estimated by fitting an exponential function to the

signal intensity, skipping the first echo, with the following equation: SI(TE) ~ exp(–TE/T2), where SI(TE) is the signal intensity as a function of echo time, and T2 is the transverse relaxation time[24,25]. A monoexponential decay model was used as previously described[13]. The mean T2 value for the tibiofemoral joint was calculated by averaging the T2 values of the LFC, MFC, LT, and MT. The average T2 value of the entire knee joint was calculated by averaging the mean T2 values of all five compartments.

A prior T2 relaxation time reproducibility study using this segmentation technique found minimal intra-reader reproducibility errors in the OAI, with the following RMS reproducibility errors by compartment: lateral femur (LF) 1.52%, LT 1.02%, medial femur (MF) 1.18%, MT 2.36%, Pat 1.19%, and mean of all compartments 1.46%[26]. For inter-reader reproducibility, the mean T2 RMS error by compartment were as follows: LF 1.39%, LT 1.86%, MF 1.63%, MT 1.45%, Pat 1.22%, and mean of all compartments 1.57%[26].

Physical activity levels

Physical activity levels were measured using the PASE, a well-established and reliable questionnaire that has been validated in older and younger individuals[13,27,28]. The PASE consists of a numerical score and assesses three domains of physical activity over a period of 7 days, including household, occupational, and leisure activities. Subjects completed the questionnaire at baseline, then annually over a 4-year period, allowing for a total of five PASE scores per patient. For each subject, the PASE scores collected over five time points were averaged and categorized into tertiles: tertile 1 (PASE 31–152), tertile 2 (PASE 153–207), tertile 3 (PASE 208–368). All subjects had a PASE score and no subjects were excluded. To more thoroughly analyze the relationship between PASE scores and T2 values by targeting the extremes of physical activity, we also created an alternate classification: (1) highest 15% PASE scores (PASE 242–368), (2) lowest 15% PASE scores (PASE 31–120), and (3) middle 70% PASE scores (PASE 124–242). Sample size calculations required a minimum of thirty subjects in each group to detect a difference of at least 1 msec in T2 values between physical activity groups and allow for statistical power of at least 0.80. Consequently, the highest and lowest 15% PASE scores were chosen as the cut-off. In addition, we chose not to simply use baseline PASE values because the score assesses physical activity only over 7 days and averaging the PASE scores over 4 years provided a better approximation of physical activity levels.

However, limitations of using the mean PASE score over 4 years are the inability to account for changes in PASE over time and to use PASE to predict current T2 values. We therefore also fitted a longitudinal statistical model using the current value of PASE as a predictor. Since we expected a non-monotonic relationship between PASE and the outcomes, we fitted a quadratic relationship between PASE and T2.

Statistical analysis

Statistical analysis for this study was performed using JMP version 7 software (SAS institute) and STATA version 12 software. For subject characteristics, differences in numerical variables such as age, BMI, and mean PASE were determined using the Kruskal–Wallis test. For categorical variables such as gender, cohort, and risk factors (i.e., history of knee injury, history of knee surgery, family history of knee replacement, and Heberden's nodes in hands), chi-squared tests were used to compare differences between physical activity groups. We used Wilcoxon signed rank tests to compare differences between baseline and 48-month T2 values in each of the physical activity groups. A mixed model linear regression was used to determine significant differences in T2 values between PASE tertiles and between groups based on the highest and lowest 15% PASE scores. Covariates included age, sex, BMI, cohort, each individual, physical activity level, and physical activity

level crossed with time point (baseline, 24-month, 48-month). We assigned the individual as a random effect, assuming an equal correlation within a person over time, and the other covariates as fixed effects. *P* values less than 0.05 were considered significant.

Results

Subject characteristics

Table I lists the subject characteristics, including age, gender, and risk factors, organized by physical activity level (Low activity, $n = 69$; Moderate activity, $n = 68$, High activity, $n = 68$). Subjects of different physical activity levels did not significantly differ in gender, OAI cohort, risk factors, and baseline BMI. Only age showed significant differences between the three physical activity groups using analysis of variance ($P < 0.001$). During statistical analysis, we adjusted for age, gender, cohort, BMI, and included random effects for each individual in a mixed model linear regression.

Physical activity level by PASE tertile

All physical activity groups showed significant progression of T2 values over the 4-year time period ($P < 0.001$). At each time point, the MF displayed the highest T2 values, while the LT showed the lowest T2 values. In all physical activity groups, T2 progression was highest at the Pat, and lowest at the MF. In the first part of the analysis, we categorized subjects into three groups using PASE tertiles (low, moderate, high physical activity). Over the 48-month follow-up period, T2 values of the higher physical activity group progressed more than the T2 values of the moderate physical activity group in all compartments, with significance observed at the MT [0.44 (0.03–0.85) (95% confidence interval) ms, $P = 0.041$], the Pat [0.70 (0.13–1.27) ms, $P = 0.019$], and when T2 values of all compartments were averaged [0.30 (0.03–0.57) ms, $P = 0.033$] (Table II). T2 values of the low physical activity group also progressed more than T2 values of the moderate physical activity group, but differences were not significant. The moderate physical activity group consistently showed the lowest T2 values at baseline and 48-month follow-up (Fig. 2, Table III).

Extremes in physical activity

To analyze the association between extremes in physical activity and T2 progression, we categorized subjects into three groups using an alternate classification: (1) 15% of subjects with the highest PASE scores, (2) 15% of subjects with the lowest PASE scores, and (3) 70% of subjects who fell in between the first two groups (very low, medium, and very high physical activity). Using this classification, T2 values of the highest physical activity group progressed more than the mid-physical activity group in all compartments over the 48-month follow-up period, with significance observed in the LT [0.60 (0.15–1.05) ms, $P = 0.009$], MT [0.52 (0.03–1.01) ms, $P = 0.037$], and average of all compartments [0.33 (0.02–0.49) ms, $P = 0.043$] (Table IV). The lowest physical activity group also showed more T2 progression than the middle physical activity group in all compartments, with significance in the LF [0.46 (0.05–0.87) ms, $P = 0.025$], LT [0.46 (0.01–0.91) ms, $P = 0.043$), MF [0.42 (0.01–0.83) ms, $P = 0.044$], tibiofemoral compartment [0.41 (0.08–0.74) ms, $P = 0.017$], patellofemoral compartment [0.46 (0.09–0.83) ms, $P = 0.016$), lateral compartments [0.66 (0.23–1.09) ms, $P = 0.003$], and average of all compartments [0.32 (0.01–0.64) ms, $P = 0.043$] (Table IV).

Current PASE in relation to changes in T2 relaxation time

We also performed a secondary analysis to account for dynamic changes in PASE over the 4 years. We examined the relationship between the concurrent PASE, in both linear and quadratic forms, and T2 relaxation time at each time point. Using this analysis, all

compartments of the knee yielded a negative coefficient for the linear form of current PASE and a positive coefficient for the quadratic form of current PASE, with significance found at the MT (overall fixed $P = 0.01$) (Table V). Consistent with our expectations, this demonstrates a quadratic relationship between PASE values and T2 relaxation time over 4 years with T2 values decreasing for lower values of PASE and then increasing. The middle interval of PASE scores (PASE scores around 200) yielded the lowest T2 values, while the lower and higher intervals of PASE scores yielded the highest T2 values (Fig. 3).

Discussion

In this longitudinal cohort study, subjects with high PASE scores showed higher progression of T2 relaxation time than in subjects with moderate PASE scores. When stratified into groups of extreme physical activity, subjects exposed to both very low and very high PASE scores demonstrated higher progression of T2 values compared to subjects with mid-level PASE scores. Our findings suggest that both sedentary lifestyles and higher levels of physical activity may be associated with worsened biochemical changes in the cartilage matrix, especially in subjects who have OA risk factors.

To the best of our knowledge, this is the first longitudinal study to evaluate the relationship between physical activity and MRI-based molecular changes in cartilage, a potential precursor to OA. In two cross-sectional studies analyzing the association between recreational exercise levels and T2 relaxation time, light exercisers showed lower T2 values than vigorous exercisers[13,14]. Other studies have also explored the longitudinal association between physical activity and OA, but results have been contradictory[29–31]. Teichtahl *et al.* found that subjects who participated in vigorous physical activity showed a lower rate of patellar cartilage volume loss over 2 years, suggesting that vigorous physical activity may be beneficial to the patella-femoral joint[31]. On the contrary, Wang et al. found that participation in vigorous activity was associated with a risk of primary knee replacement due to OA[29]. In another study, subjects who performed ≥10,000 steps/day had a greater risk of increasing meniscus and cartilage defects, especially in those with pre-existing knee structural abnormalities[32]. In these studies, the measured outcomes, such as loss of cartilage thickness, OA symptoms, and surgery, are irreversible in the natural course of OA. Our study analyzes physical activity in context of biochemical changes in cartilage that may still be reversible with prevention and behavioral modification.

Our findings generate a hypothesis that there may exist an optimal level of physical activity. Perhaps moderation of certain types of physical activities may yield the least amount of acceleration toward OA compared to sedentary and very active lifestyles[27]. Our longitudinal data are consistent with prior cross-sectional studies. Hovis *et al.* and Stehling *et al.* similarly reported an association between high physical activity levels and elevated T2 values at the Pat, LT, and tibiofemoral joint[13,14]. In addition, Luke *et al.* reported that the patellofemoral joint and medial compartment of the knee showed the greatest changes in T2 after running and therefore, were at highest risk of degenerating with physical activity[33]. The compartments in our study found to be statistically significant, the MT and Pat, are consistent with these results. We performed a secondary analysis examining the association between dynamic changes in PASE and T2 relaxation time in T2 relaxation time, and similarly observed a significant quadratic relationship at the MT.

The mechanism for how physical activity impacts the biochemical composition of cartilage remains controversial. The accelerated T2 progression in our sedentary subjects was present in several compartments, and may reflect an absence of joint loading, which is important for proper cartilage development and function[34]. Vanwanseele *et al.* examined patients with complete, traumatic spinal cord injury and found atrophy at the Pat and MT cartilage in the

absence of normal joint loading[35]. Others propose that weakness in the quadriceps muscle, a potential sequela of inactivity, may also disrupt joint stability and cause subsequent cartilage loss[36,37]. Our subjects with high physical activity levels also demonstrated accelerated T2 progression. Though controversial, physical activity may impart excessive forces on the joint and compromise structural integrity, especially in subjects at risk for OA, similar to those found in the incidence cohort[38–41]. Our findings of accelerated T2 progression in these groups are potentially noteworthy because biochemical degeneration of cartilage occurs at a stage that may still be reversible. Studies have shown that changes in T2 relaxation time are in part due to degradation of the type II collagen matrix[42]. This raises concern whether T2 measurements indeed detect cartilage degeneration at a stage where damage is still reversible. However, previous studies have shown that cartilage and meniscus T2 values were significantly greater in runners shortly after running a marathon, but normalized 3 months later[33,43]. This data suggests that changes in T2, especially due to physically activity, may be also caused by transient fluid changes and therefore, may still be reversible.

There are several limitations in our study. First, while the PASE questionnaire accounts for a variety of activities, it does not distinguish between weight-bearing and non-weight-bearing activities. Weight-bearing activities may exert a different effect on joint structures than non-weight-bearing activities such as swimming. Second, the averaged PASE scores over 4 years are not true predictors because they include scores taken after baseline and there is no precedent of averaging PASE scores in prior studies. However, each PASE score only accounts for 7 days of activity, and we felt that compiling 4 years worth of PASE scores would be more representative of an individual's physical activity. We also used a second statistical model to account for changes of PASE over time using the current numeric PASE values as a predictor in quadratic form. While PASE can change within a person or between people, this is the most sensitive analysis as we are expecting lowest results in the middle PASE group. Third, the predictive value of T2 relaxation time for incident osteoarthritis still remains controversial, and the inclusion of T1rho sequences would have strengthened our study. However, the OAI did not include T1rho sequences. Lastly, the variation and changes in water content of knee cartilage could have also contributed to the progression of T2 values over the 48-month period[9]. Without immunohistologic studies, we are unable to differentiate normal aging of cartilage from early changes of degenerative OA.

Future studies need to confirm our findings in other cohorts. More objective measures of physical activity, such as accelerometers, should also be used as predictors in relation to T2 values. We did not have enough patients from the OAI normal cohort to perform a longitudinal analysis by cohort, but future studies should also investigate whether physical activity impacts the biochemical changes in cartilage differently in subjects with or without OA risk factors. In addition, prior studies have also demonstrated that longer T2 values are first observed at the superficial layer of articular cartilage in subjects aged 46–65, and this lengthening of T2 progresses over the entire cartilage with age[44,45]. In future studies, depth dependent assessment of cartilage T2 will potentially provide further insight on the effect of physical activity on cartilage T2.

In summary, our findings generate a hypothesis that a moderate level of physical activity may be optimal for slowing the progression of cartilage degeneration in asymptomatic subjects. Subjects with high physical activity levels showed a significantly accelerated T2 progression, possibly from excessive loading and subsequent disruption of joint stability. A sedentary lifestyle also produced an accelerated progression of T2 values, perhaps from the absence of loading needed for healthy cartilage. Our findings parallel results from cross-sectional studies comparing physical activity to T2 relaxation time and also suggest the potential ability of T2 relaxation time to identify sedentary and physically active subjects at

most risk of OA. The results of our study should be confirmed in other cohorts and using different measures of physical activity such as step count derived from accelerometers.

Acknowledgments

Role of funding source

This study was funded by NIH U01 AR059507 and P50 AR060752 as well as through the OAI, which is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript has received the approval of the OAI Publication Committee based on a review of its scientific content and data interpretation. Otherwise, sources of funding were not involved in the design, data interpretation, or writing of manuscript of this study.

References

1. Sinusas K. Osteoarthritis: diagnosis and treatment. Am Fam Physician. Jan 1. 2012; 85(1):49–56. [PubMed: 22230308]
2. Mosher TJ, Liu Y, Torok CM. Functional cartilage MRI T2 mapping: evaluating the effect of age and training on knee cartilage response to running. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Mar; 2010 18(3):358–64.
3. Mosher TJ, Smith HE, Collins C, Liu Y, Hancy J, Dardzinski BJ, et al. Change in knee cartilage T2 at MR imaging after running: a feasibility study. Radiology. Jan; 2005 234(1):245–9. [PubMed: 15550376]
4. Spector TD, Harris PA, Hart DJ, Cicuttini FM, Nandra D, Etherington J, et al. Risk of osteoarthritis associated with long-term weight-bearing sports: a radiologic survey of the hips and knees in female ex-athletes and population controls. Arthritis Rheum. Jun; 1996 39(6):988–95. [PubMed: 8651993]
5. Cheng Y, Macera CA, Davis DR, Ainsworth BE, Troped PJ, Blair SN. Physical activity and self-reported, physician-diagnosed osteoarthritis: is physical activity a risk factor? J Clin Epidemiol. Mar 1; 2000 53(3):315–22. [PubMed: 10760643]
6. Rogers LQ, Macera CA, Hootman JM, Ainsworth BE, Blairi SN. The association between joint stress from physical activity and self-reported osteoarthritis: an analysis of the Cooper Clinic data. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Aug; 2002 10(8):617–22.
7. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. Arthritis Rheum. Nov; 2005 52(11):3507–14. [PubMed: 16258919]
8. Racunica TL, Teichtahl AJ, Wang Y, Wluka AE, English DR, Giles GG, et al. Effect of physical activity on articular knee joint structures in community-based adults. Arthritis Rheum. Oct 15; 2007 57(7):1261–8. [PubMed: 17907212]
9. Liess C, Lüsse S, Karger N, Heller M, Glüer C-C. Detection of changes in cartilage water content using MRI T2-mapping in vivo. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Dec; 2002 10(12):907–13.
10. Dunn TC, Lu Y, Jin H, Ries MD, Majumdar S. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. Radiology. Aug; 2004 232(2):592–8. [PubMed: 15215540]
11. Newbould RD, Miller SR, Toms LD, Swann P, Tielbeek JAW, Gold GE, et al. T2* measurement of the knee articular cartilage in osteoarthritis at 3T. J Magn Reson Imaging. 2012; 35(6):1422–9. [PubMed: 22314961]
12. Li X, Benjamin Ma C, Link TM, Castillo D-D, Blumenkrantz G, Lozano J, et al. In vivo T(1rho) and T(2) mapping of articular cartilage in osteoarthritis of the knee using 3 T MRI. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Jul; 2007 15(7):789–97.
13. Stehling C, Liebl H, Krug R, Lane NE, Nevitt MC, Lynch J, et al. Patellar cartilage: T2 values and morphologic abnormalities at 3.0-T MR imaging in relation to physical activity in asymptomatic

subjects from the osteoarthritis initiative. Radiology. Feb; 2010 254(2):509–20. [PubMed: 20019141]

14. Hovis KK, Stehling C, Souza RB, Haughom BD, Baum T, Nevitt M, et al. Physical activity is associated with magnetic resonance imaging-based knee cartilage T2 measurements in asymptomatic subjects with and those without osteoarthritis risk factors. Arthritis Rheum. Aug; 2011 63(8):2248–56. [PubMed: 21538328]
15. Felson DT, Nevitt MC. Epidemiologic studies for osteoarthritis: new versus conventional study design approaches. Rheum Dis Clin North Am. Nov; 2004 30(4):783–97. vii. [PubMed: 15488693]
16. Bellamy N, Buchanan WW, Goldsmith CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. J Rheumatol. Dec; 1988 15(12):1833–40. [PubMed: 3068365]
17. KELLGREN JH, LAWRENCE JS. Radiological assessment of osteoarthrosis. Ann Rheum Dis. Dec; 1957 16(4):494–502. [PubMed: 13498604]
18. Peterfy CG, Guermazi A, Zaim S, Tirman PFJ, Miaux Y, White D, et al. Whole-Organ Magnetic Resonance Imaging Score (WORMS) of the knee in osteoarthritis. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Mar; 2004 12(3):177–90.
19. Peterfy CG, Schneider E, Nevitt M. The osteoarthritis initiative: report on the design rationale for the magnetic resonance imaging protocol for the knee. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Dec; 2008 16(12):1433–41.
20. Schneider E, Nessaiver M. The Osteoarthritis Initiative (OAI) magnetic resonance imaging quality assurance update. Osteoarthritis Cartilage OARS Osteoarthritis Res Soc. Jan; 2013 21(1):110–6.
21. Lerski RA, McRobbie DW, Straughan K, Walker PM, de Certaines JD, Bernard AM. Multi-center trial with protocols and prototype test objects for the assessment of MRI equipment. EEC Concerted Research Project. Magn Reson Imaging. Apr; 1988 6(2):201–14. [PubMed: 3374294]
22. Carballido-Gamio J, Bauer JS, Stahl R, Lee K-Y, Krause S, Link TM, et al. Inter-subject comparison of MRI knee cartilage thickness. Med Image Anal. Apr; 2008 12(2):120–35. [PubMed: 17923429]
23. Carballido-Gamio J, Majumdar S. Atlas-based knee cartilage assessment. Magn Reson Med Off J Soc Magn Reson Med Soc Magn Reson Med. Aug; 2011 66(2):574–83.
24. Smith HE, Mosher TJ, Dardzinski BJ, Collins BG, Collins CM, Yang QX, et al. Spatial variation in cartilage T2 of the knee. J Magn Reson Imaging JMRI. Jul; 2001 14(1):50–5.
25. Maier CF, Tan SG, Hariharan H, Potter HG. T2 quantitation of articular cartilage at 1.5 T. J Magn Reson Imaging JMRI. Mar; 2003 17(3):358–64.
26. Stehling C, Baum T, Mueller-Hoecker C, Liebl H, Carballido-Gamio J, Joseph GB, et al. A novel fast knee cartilage segmentation technique for T2 measurements at MR imaging – data from the Osteoarthritis Initiative. Osteoarthritis Cartilage. Aug; 2011 19(8):984–9. [PubMed: 21515391]
27. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. Feb; 1993 46(2):153–62. [PubMed: 8437031]
28. Goldstein MG, Pinto BM, Marcus BH, Lynn H, Jette AM, Rakowski W, et al. Physician-based physical activity counseling for middle-aged and older adults: a randomized trial. Ann Behav Med Publ Soc Behav Med. 1999; 21(1):40–7.
29. Wang Y, Simpson JA, Wluka AE, Teichtahl AJ, English DR, Giles GG, et al. Is physical activity a risk factor for primary knee or hip replacement due to osteoarthritis? A prospective cohort study. J Rheumatol. Feb; 2011 38(2):350–7. [PubMed: 20952471]
30. Michaëlsson K, Byberg L, Ahlbom A, Melhus H, Farahmand BY. Risk of severe knee and hip osteoarthritis in relation to level of physical exercise: a prospective cohort study of long-distance skiers in Sweden. Plos One. 2011; 6(3):e18339. [PubMed: 21479136]
31. Teichtahl AJ, Wluka AE, Forbes A, Wang Y, English DR, Giles GG, et al. Longitudinal effect of vigorous physical activity on patella cartilage morphology in people without clinical knee disease. Arthritis Rheum. Aug 15; 2009 61(8):1095–102. [PubMed: 19644895]

32. Doré DA, Winzenberg TM, Ding C, Otahal P, Pelletier J-P, Martel-Pelletier J, et al. The association between objectively measured physical activity and knee structural change using MRI. Ann Rheum Dis. Jul; 2013 72(7):1170–5. [PubMed: 22896739]
33. Luke AC, Stehling C, Stahl R, Li X, Kay T, Takamoto S, et al. High-field magnetic resonance imaging assessment of articular cartilage before and after marathon running: does long-distance running lead to cartilage damage? Am J Sports Med. Nov; 2010 38(11):2273–80. [PubMed: 20631252]
34. Jones G, Ding C, Glisson M, Hynes K, Ma D, Cicuttini F. Knee articular cartilage development in children: a longitudinal study of the effect of sex, growth, body composition, and physical activity. Pediatr Res. Aug; 2003 54(2):230–6. [PubMed: 12736391]
35. Vanwanseele B, Eckstein F, Knecht H, Stüssi E, Spaepen A. Knee cartilage of spinal cord-injured patients displays progressive thinning in the absence of normal joint loading and movement. Arthritis Rheum. Aug; 2002 46(8):2073–8. [PubMed: 12209511]
36. Slemenda C, Brandt KD, Heilman DK, Mazzuca S, Braunstein EM, Katz BP, et al. Quadriceps weakness and osteoarthritis of the knee. Ann Intern Med. Jul 15; 1997 127(2):97–104. [PubMed: 9230035]
37. Slemenda C, Heilman DK, Brandt KD, Katz BP, Mazzuca SA, Braunstein EM, et al. Reduced quadriceps strength relative to body weight: a risk factor for knee osteoarthritis in women? Arthritis Rheum. Nov; 1998 41(11):1951–9. [PubMed: 9811049]
38. Lin J, Li R, Kang X, Li H. Risk factors for radiographic tibiofe-moral knee osteoarthritis: the wuchuan osteoarthritis study. Int J Rheumatol. 2010; 2010:385826. [PubMed: 21234318]
39. Verweij LM, van Schoor NM, Deeg DJH, Dekker J, Visser M. Physical activity and incident clinical knee osteoarthritis in older adults. Arthritis Rheum. Feb 15; 2009 61(2):152–7. [PubMed: 19177523]
40. Stahl R, Luke A, Li X, Carballido-Gamio J, Ma CB, Majumdar S, et al. T1rho, T2 and focal knee cartilage abnormalities in physically active and sedentary healthy subjects versus early OA patientsea 3.0-Tesla MRI study. Eur Radiol. Jan; 2009 19(1):132–43. [PubMed: 18709373]
41. Cibere J, Zhang H, Thorne A, Wong H, Singer J, Kopec JA, et al. Association of clinical findings with pre-radiographic and radiographic knee osteoarthritis in a population-based study. Arthritis Care Res. Dec; 2010 62(12):1691–8.
42. Hollander AP, Pidoux I, Reiner A, Rorabeck C, Bourne R, Poole AR. Damage to type II collagen in aging and osteoarthritis starts at the articular surface, originates around chondrocytes, and extends into the cartilage with progressive degeneration. J Clin Invest. Dec; 1995 96(6):2859–69. [PubMed: 8675657]
43. Stehling C, Luke A, Stahl R, Baum T, Joseph G, Pan J, et al. Meniscal T1rho and T2 measured with 3.0 T MRI increases directly after running a marathon. Skeletal Radiol. Jun; 2011 40(6):725–35. [PubMed: 21052658]
44. Mosher TJ, Liu Y, Yang QX, Yao J, Smith R, Dardzinski BJ, et al. Age dependency of cartilage magnetic resonance imaging T2 relaxation times in asymptomatic women. Arthritis Rheum. Sep; 2004 50(9):2820–8. [PubMed: 15457450]
45. Mosher TJ, Dardzinski BJ, Smith MB. Human articular cartilage: influence of aging and early symptomatic degeneration on the spatial variation of T2–preliminary findings at 3 T. Radiology. Jan; 2000 214(1):259–66. [PubMed: 10644134]

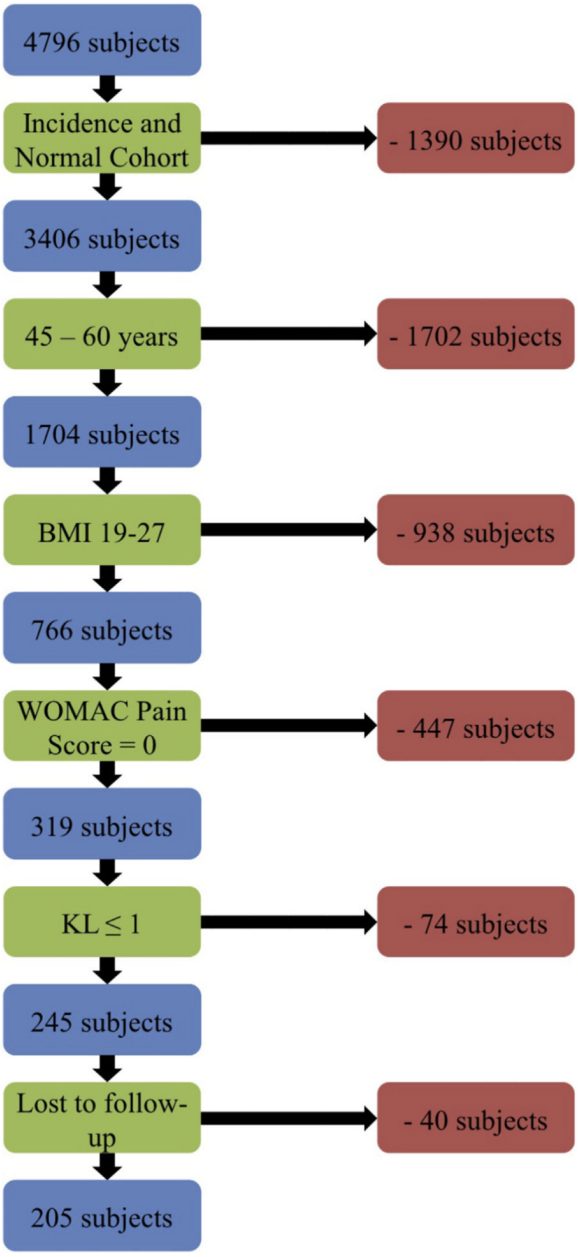

Fig. 1.
Schematic illustration showing selection of subjects. 40 normal cohort subjects and 165 incidence cohort subjects fulfilled the inclusion and exclusion criteria.

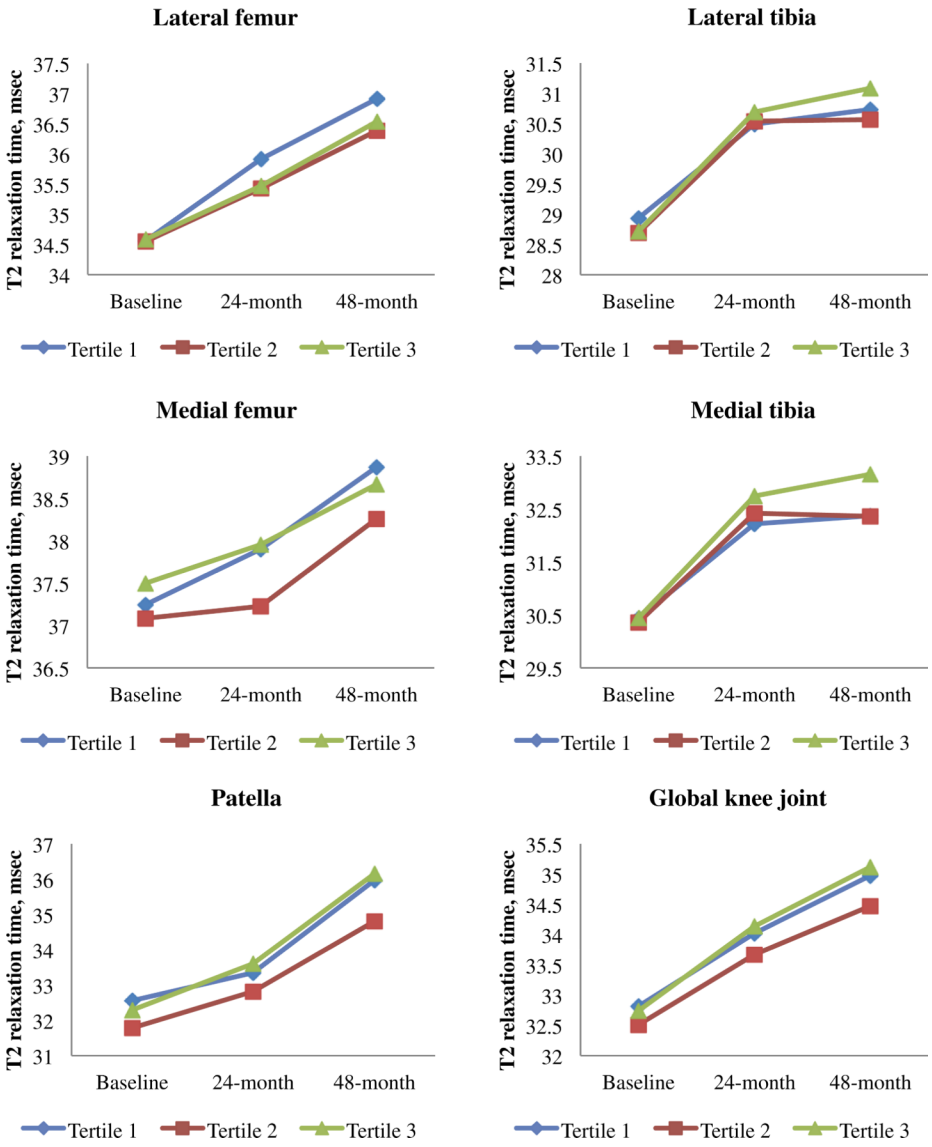

Fig. 2.

Longitudinal T2 values over 48 months by compartment. Subjects in the moderate physical activity group overall show the lowest progression of T2 relaxation time over the 48-month time period. Tertiles are based on PASE scores.

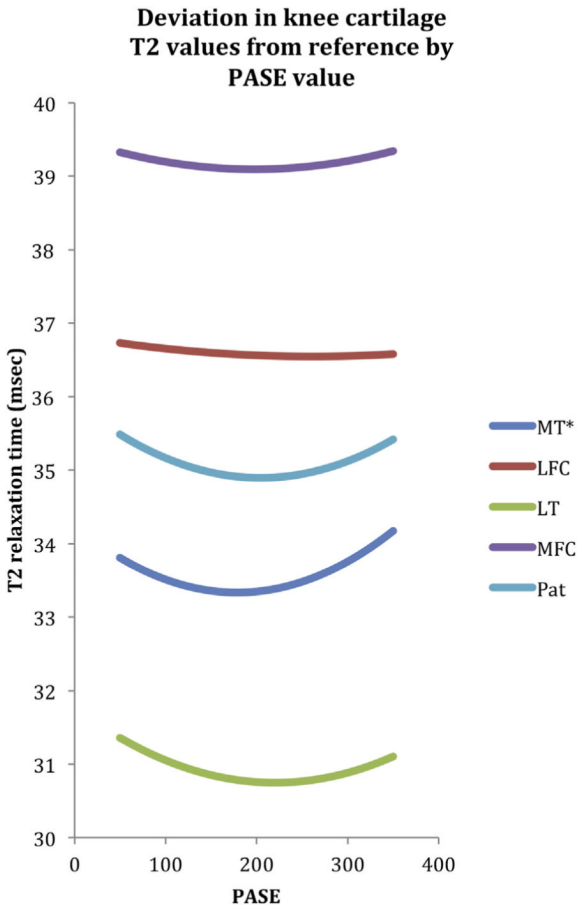

Fig. 3.

Graph demonstrating the estimated quadratic relationship between PASE scores and T2 relaxation time for a reference individual at 48-month follow-up with the following characteristics: age = 50, BMI = 23, cohort = Incidence, sex = Male. *Statistically significant ($P < 0.05$).

Table I

Subject characteristics

	All subjects	Physical activity classification*		
		Low	Moderate	High
	n **= 205**	***n*** **= 69**	***n*** **= 68**	***n*** **= 68**
Gender				
Male	81	21	29	31
Female	124	48	39	37
Cohort				
Incidence	165	56	52	57
Normal	40	13	8	11
Risk factors, no. (%)				
History of knee injury	56 (27)	19 (28)	19 (28)	18 (26)
History of knee surgery	15 (7)	4(5)	6 (9)	5 (7)
Family history of knee replacement	30 (15)	9 (13)	9 (13)	12 (18)
Heberden's nodes in hands	48 (23)	22 (32)	12 (18)	14(21)
Age, years at baseline†	52.8 ± 4.0	54.3 ± 3.9	51.7 ± 3.9	52.4 ± 3.9‡
BMI, kg/m^2 at baseline†	23.7 ± 2.2	23.5 ± 2.3	23.7 ± 2.3	23.7 ± 2.1
Mean PASE over 4 years†	182.8 ± 60.8	118.3 ± 28.8	181.7 ± 16.3	249.4 ± 37.0‡

*Low = PASE tertile 1 (PASE range 31–152); Moderate = PASE tertile 2 (PASE range 153–207); High = PASE tertile 3 (PASE range 208–368).

†Values are mean ± standard deviation.

‡$P < 0.001$ by analysis of variance.

Table II

T2 progression over 4-year time period by PASE tertile*

T2 progression, msec	Exercise classification†		
	Low	Moderate	High
	n = 69	*n* = 68	*n* = 68
Lateral femoral condyle	2.68 (2.19–3.17)	2.20 (1.69–2.71)	2.43 (1.94–2.92)
Lateral tibia	2.05 (1.44–2.66)	1.82 (1.23–2.41)	2.23 (1.60–2.86)
Medial femoral condyle	1.58 (1.09–2.07)	1.18 (0.69–1.67)	1.39 (0.88–1.90)
Medial tibia	2.12 (1.57–2.67)	1.98 (1.43–2.53)	2.79 (2.24–3.34)‡
Patella	3.56 (2.68–4.44)	3.10 (2.18–4.02)	4.10 (3.22–4.98)§
Tibiofemoral joint	2.12 (1.71–2.53)	1.72 (1.31–2.13)	2.15 (1.74–2.56)
Patellofemoral joint	2.60 (1.80–3.40)	1.61 (0.81–2.41)	2.73 (1.93–3.53)
Lateral compartment	2.64 (1.86–3.42)	1.71 (0.95–2.47)	2.05 (1.27–2.83)
Medial compartment	1.89 (1.42–2.36)	1.59 (1.12–2.06)	2.25 (1.78–2.72)
Global knee joint	2.41 (2.04–2.78)	1.96 (1.59–2.33)	2.53 (2.16–2.90)‖

*Values are least square mean (95% confidence interval) ms. Differences between groups were determined by mixed model linear regression analysis adjusted for age, sex, body mass index, OAI cohort, and random effects for each individual.

†Low = PASE tertile 1; Moderate = PASE tertile 2; High = PASE tertile 3.

‡High > Moderate by 0.44 (0.03–0.85) ms, $P = 0.041$.

§High > Moderate by 0.70 (0.13–1.27) ms, $P = 0.019$.

‖High > Moderate by 0.30 (0.03–0.57) ms, $P = 0.033$.

Table III

T2 relaxation time at three different time points by physical activity level*

Physical activity level†	Baseline			24-month			48-month		
	Low	Moderate	High	Low	Moderate	High	Low	Moderate	High
Compartment									
Lateral femur	34.6 (34.0–35.1)	34.5 (34.0–35.1)	34.6 (34.1–35.1)	35.9 (35.4–36.4)	35.5 (34.9–36.0)	35.5 (35.0–36.0)	37.0 (36.5–37.5)	36.5 (36.0–36.9)	36.6 (36.2–37.1)
Lateral tibia	29.0 (28.4–29.5)	28.6 (28.1–29.2)	28.7 (28.2–29.2)	30.5 (30.0–31.0)	30.5 (30.0–31.1)	30.7 (30.2–31.2)	30.8 (30.2–31.4)	30.6 (30.0–31.1)	31.1 (30.5–31.6)
Medial femur	37.2 (36.7–37.8)	37.1 (36.6–37.6)	37.5 (36.9–38.1)	37.9 (37.2–38.5)	37.5 (36.8–38.1)	38.2 (37.6–38.7)	38.9 (38.2–39.5)	38.3 (37.7–38.8)	38.7 (38.2–39.3)
Medial tibia	30.4 (29.9–31.0)	30.4 (29.8–30.9)	30.4 (29.9–31.0)	32.3 (31.8–32.8)	32.5 (31.9–33.0)	32.8 (32.2–33.3)	32.4 (31.9–32.9)	32.4 (31.9–32.9)	33.2 (32.7–33.7)
Patella	32.6 (31.9–33.2)	31.7 (30.8–32.5)	32.3 (31.7–32.9)	33.5 (32.9–34.1)	32.9 (32.2–33.6)	33.5 (32.8–34.2)	36.0 (35.2–36.7)	34.6 (33.9–35.2)	36.2 (35.4–37.0)

*Values are mean (95% confidence interval) ms.

†Low = PASE tertile 1; Moderate = PASE tertile 2; High = PASE tertile 3.

Table IV

T2 progression over 4-year period by upper and lower 15% PASE[†]

T2 progression, msec	Exercise classification[†]			*P*-value	
	Very low	Medium	Very high		
	n = 31	*n* = 143	*n* = 31		
				Very low vs medium	Very high vs medium
Lateral femoral condyle	3.08 (2.39–3.77)	2.25 (1.88–2.62)	2.52 (1.83–3.21)	**0.025**	0.466
Lateral tibia	2.89 (2.09–3.69)	1.71 (1.26–2.16)	2.48 (1.66–3.30)	**0.043**	**0.009**
Medial femoral condyle	1.97 (1.28–2.66)	1.24 (0.87–1.61)	1.39 (0.66–2.12)	**0.044**	0.931
Medial tibia	2.33 (1.55–3.11)	2.16 (1.75–2.57)	2.77 (1.99–3.55)	0.548	**0.037**
Patella	3.65 (2.47–4.83)	3.46 (2.75–4.17)	4.09 (2.87–5.31)	0.540	0.316
Tibiofemoral joint	2.53 (1.96–3.10)	1.81 (1.50–2.12)	2.19 (1.62–2.76)	**0.017**	0.072
Patellofemoral joint	2.85 (1.75–3.95)	2.05 (1.44–2.66)	2.84 (1.72–3.96)	**0.016**	0.334
Lateral compartment	3.85 (2.79–4.91)	1.70 (1.11–2.29)	2.15 (1.09–3.21)	**0.003**	0.080
Medial compartment	2.20 (1.53–2.87)	1.72 (1.35–2.09)	2.39 (1.72–3.06)	0.296	0.076
Global knee joint	2.72 (2.21–3.23)	2.11 (1.84–2.38)	2.61 (2.10–3.12)	**0.043**	**0.043**

Significant *P*-values in bold.

[†]Values are least square mean (95% confidence interval) ms. Differences between groups were determined by mixed model linear regression analysis adjusted for age, sex, body mass index, OAI cohort, and random effects for each individual.

[†]Very low = lowest 15% PASE scores; Very high = highest 15% PASE scores; Medium = Middle 70% PASE scores.

Table V

The association between T2 relaxation time and the concurrent PASE at each time point, in linear and quadratic form*

Compartment	Variable	Coefficient	*P*-value	Overall *P*-value†
Lateral femoral condyle	Current PASE	-2.14×10^{-3}	0.55	0.77
	Current PASE^2	4.10×10^{-6}	0.47	
Lateral tibia	Current PASE	-9.29×10^{-3}	0.02y	0.05
	Current PASE^2	2.11×10^{-5}	0.02y	
Medial femoral condyle	Current PASE	-4.22×10^{-3}	0.24	0.47
	Current PASE^2	1.07×10^{-5}	0.22	
Medial tibia	Current PASE	-1.01×10^{-2}	0.01 y	**0.01**
	Current PASE^2	2.86×10^{-5}	0.01 y	
Patella	Current PASE	-1.01×10^{-2}	0.07	0.19
	Current PASE^2	2.46×10^{-5}	0.07	
Tibiofemoral joint	Current PASE	-3.91×10^{-3}	0.19	0.41
	Current PASE^2	9.09×10^{-6}	0.21	
Patellofemoral joint	Current PASE	-3.01×10^{-3}	0.36	0.66
	Current PASE^2	7.05×10^{-6}	0.38	
Lateral compartment	Current PASE	-3.52×10^{-3}	0.34	0.57
	Current PASE^2	7.20×10^{-6}	0.42	
Medial compartment	Current PASE	-6.73×10^{-3}	0.05	0.15
	Current PASE^2	1.57×10^{-5}	0.06	
Global knee joint	Current PASE	-4.36×10^{-3}	0.11	0.28
	Current PASE^2	1.04×10^{-5}	0.12	

Significant *P*-values in bold.

*Negative linear and positive quadratic coefficients demonstrate the quadratic relationship between PASE and longitudinal change in T2. A mixed model linear regression was used, adjusting for age, sex, body mass index, OAI cohort, and random effects for each individual.

†Represents fixed effect test for both Current PASE and Current PASE^2 combined.