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Association of Physical Activity Measured by Accelerometer, Knee Joint Abnormalities, and Cartilage T2 Measurements Obtained From 3T Magnetic Resonance Imaging: Data From the Osteoarthritis Initiative

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Objective. To study the cross-sectional association between physical activity measured with an accelerometer, structural knee abnormalities, and cartilage T2 values assessed with 3T magnetic resonance imaging (MRI).
Methods. We included 274 subjects from the Osteoarthritis Initiative cohort without definite radiographic osteoarthritis (Kellgren/Lawrence grades 0 and 1) and with at most mild pain, stiffness, and functional limitation in the study knee (Western Ontario and McMaster Universities Osteoarthritis Index scale 0–1), which had not limited their activity due to knee pain. Physical activity was measured over 7 days with an ActiGraph GT1M accelerometer. Subjects were categorized by quartile of physical activity based on the average daily minutes of moderate to vigorous physical activity (mv-PA). MRI images of the right knee (at 48-month visit) were assessed for structural abnormalities using a modified Whole-Organ Magnetic Resonance Imaging Score (WORMS) and for T2 relaxation times derived from segmented cartilage of 4 femorotibial regions and the patella. WORMS grades and T2 measurements were compared between activity quartiles using a linear regression model. Covariates included age, sex, body mass index, knee injury, family history of knee replacement, knee symptoms, hip and ankle pain, and daily wear time of the accelerometer.
Results. Higher mv-PA was associated with increased severity ($P = 0.0087$) and number of lesions of the medial meniscus ($P = 0.0089$) and with severity of bone marrow edema lesions ($P = 0.0053$). No association between cartilage lesions and mv-PA was found. T2 values of cartilage (loss, damage, and abnormalities) tended to be greater in the higher quartiles of mv-PA, but the differences were nonsignificant.
Conclusion. In knees without radiographic osteoarthritis in subjects with no or mild knee pain, higher physical activity levels were associated with increases in meniscal and bone marrow edema pattern lesions.

INTRODUCTION

Since morphologic cartilage degeneration in osteoarthritis (OA) is progressive and irreversible, the identification of modifiable risk factors is essential to delay the development of the disease. Physical activity (PA) of certain types and intensity may increase the risk of developing knee OA, but the evidence for this risk is conflicting. Persons having occupations with repetitive knee bending (1,2) and elite runners or soccer players (3,4) have an increased risk of knee OA, though the latter may be due to sport-related injuries. Some studies have suggested that moderate levels of PA in the general population are associated with an increased risk of radiographic knee OA or knee replacement (5,6), but other studies have not found this association (7,8).

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Significance & Innovations

- This is the first study comparing structural and quantitative magnetic resonance imaging measures of knee joint degeneration between subjects with different levels of physical activity, objectively measured with an accelerometer.
- Higher levels of moderate to vigorous physical activity are associated with an increased severity of lesions of the medial meniscus and with more severe bone marrow edema.
- Quantitative and structural changes of the cartilage were not associated with levels of moderate to vigorous physical activity.

While most studies of PA and knee OA have assessed disease with radiographs, recent studies (9–11) have used magnetic resonance imaging (MRI). MRI can assess structural abnormalities of the knee joint and can provide information on the biochemical composition of the cartilage matrix by quantifying water content, collagen integrity, and proteoglycan content using T2 and T1ρ relaxation time measurements (12,13). Some MRI studies suggest that moderate and vigorous PA (mv-PA) may have beneficial effects on cartilage volume (14) and composition (15). In contrast, in an analysis of subjects without knee pain from the Osteoarthritis Initiative (OAI), we have found an increased prevalence of lesions seen on MRI in cartilage, meniscus, and subchondral bone, increased joint effusion (16,17), and higher mean tibiofemoral T2 relaxation times (18) in most active individuals, suggesting that higher PA levels may be associated with increased joint tissue degradation.

All of these studies assessed PA by questionnaires, which are prone to a reporting bias, leading to an overestimation of PA (19). In the only study to our knowledge that has used objective measures of PA, Doré et al (20) examined longitudinal changes in MRI findings and found no difference in new cartilage lesions in subjects who performed ≥10,000 steps/day by pedometer compared to those with fewer steps. However, the more active subjects had an increased incidence of bone marrow lesions and worsening of meniscal damage, especially in those with preexisting knee structural abnormalities.

Because PA is a modifiable behavior, is recommended in treatment guidelines for the nonpharmacologic management of knee pain (21), may lessen disability (22), and might be beneficial for cartilage protection (23,24), it is important to gain a better understanding of the relationship of objectively measured PA and knee health using MRI. To do so, we used the OAI clinical data, radiographs,

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and 3T knee MRIs with a T2 mapping sequence (25), in addition to data from an OAI ancillary study of PA, assessed objectively with accelerometers (26,27). Using this data set, we evaluated the cross-sectional association of PA with knee structural abnormalities and cartilage T2 relaxation times in knees without radiographic OA, in subjects who had no, or at most mild, knee symptoms and who had not limited or reduced their physical activities due to knee pain.

MATERIALS AND METHODS

Subjects. Data are from the OAI, a longitudinal observational multicenter study of the natural evolution of knee OA in 4,796 subjects, sponsored by the NIH. Details of the study protocol are available at www.oai.ucsf.edu. The study was compliant with the Helsinki Declaration, and all subjects included in the study provided informed consent. The study protocol, amendments, and informed consent documentation were reviewed and approved by the local institutional review boards. Participants recruited at 5 clinical sites either had symptomatic knee OA (progression subcohort) or were at increased risk of developing it due to risk factors (incidence subcohort). A small number of subjects without knee pain, radiographic OA, or risk factors were also enrolled (control subcohort) (25,28). An ancillary study of PA assessed by accelerometer began at the 48-month followup visit (26,27). We used imaging and clinical data from this visit for the analysis. A subset of 274 subjects was selected for our study, using the following inclusion criteria at the 48-month visit: ages <70 years, a Kellgren/Lawrence (K/L) grade of ≤1 in the right knee, and K/L grade of ≤2 in the left knee. In addition, each question of the 3 Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (29) subscales for pain (5 questions), stiffness (2 questions), and disability (17 questions) had to be answered with a score of ≤1 (mild) for all questions in both knees. Only participants who reported that they had not limited or reduced their activities due to knee pain in the past 30 days at both the 36-month and 48-month visits were included. Subjects with rheumatoid arthritis, MRI contraindications, and incomplete data were excluded from the OAI (Figure 1). Of the 274 included subjects, 272 had risk factors for knee OA, and 2 were from the control subcohort without risk factors.

Imaging. *Radiographs and MRI protocol.* Knee radiographs were acquired at 48 months using the fixed-flexion protocol (30) and read for K/L grade as previously described (31). MRI images of the right knee were obtained using 4 identical 3T scanners (Trio, Siemens) and quadrature transmit-receive coils (USA Instruments) at 1 of 4 sites (Ohio State University, Columbus; University of Maryland School of Medicine, Baltimore; University of Pittsburgh, Pittsburgh, Pennsylvania; and Memorial Hospital of Rhode Island, Pawtucket). Details of the acquisition protocol have been published (32) and included the following sequences: coronal proton density–weighted fast spin-echo, sagittal 3-dimensional (3-D) dual echo in the steady state with selective water excitation, sagittal intermediate-weighted fast
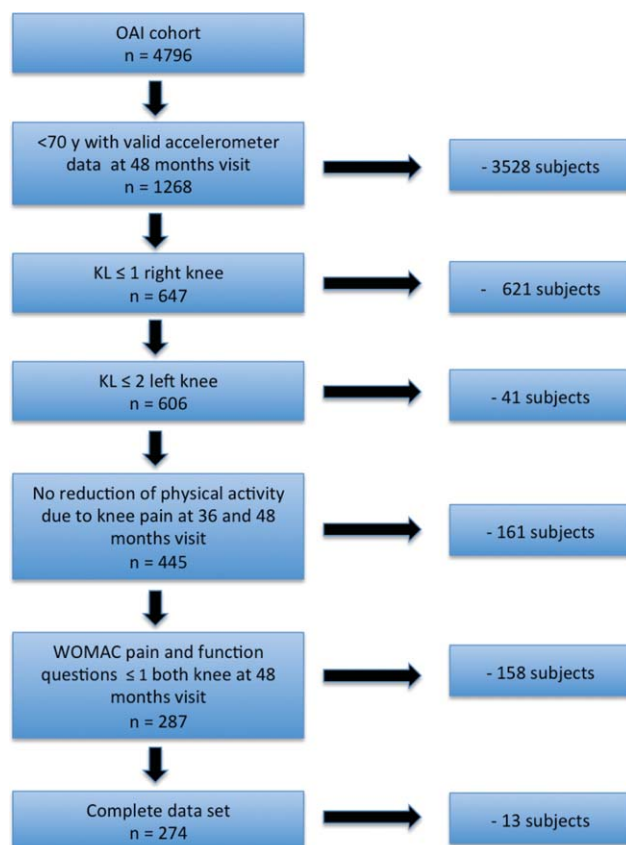
Figure 1. Patient selection according to the inclusion criteria. OAI = Osteoarthritis Initiative; y = years; KL = Kellgren/Lawrence grade; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index. Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/doi/10.1002/acr.22586/abstract.

spin-echo with fat suppression, and sagittal T2-weighted multi-echo spin-echo.

Whole-Organ Magnetic Resonance Imaging Score (WORMS) grading. MRI images were evaluated for presence and grade of cartilage, and for meniscal and bone marrow edema pattern (BMEP) lesions using WORMS (33), modified as previously described (17). Two radiologists (MK with 11 and LN with 8 years of experience), masked to the PA data, analyzed all 274 MRI studies separately, and in case of diverging findings, consensus readings were performed with a third radiologist (TML with 22 years of experience). Meniscus lesions were graded on a scale of 0–4 in each of 6 regions (medial/lateral and anterior/body/posterior). Cartilage grades (range 0–6) and BMEP grades (range 0–3) were also scored in 6 regions (patella, trochlea, medial/lateral femur, and medial/lateral tibia). BMEP was defined as areas of poorly marginated increases in T2 signal intensity in the fat-suppressed imaging sequences. For each type of lesion (meniscus, cartilage, and BMEP), a maximum score per knee (WORMS max) was defined as the highest score in any of the regions. We also calculated a lesion score for each knee by summing the scores over all regions (WORMS sum).

Quantitative T2 relaxation time measurements. We used the sagittal 2-D multi-echo spin-echo images of the right knee for segmentation and quantification of T2 relaxation time, using an inhouse-developed spline-based, semiautomated software segmentation algorithm in MATLAB software (MathWorks) (34,35). Segmentation of the cartilage was performed on the first echo sequence to maximize signal-to-noise ratio. All segmentation was performed by 3 individuals (MK, WL, and HA) in the following compartments: patella, medial/lateral femoral condyle, and medial/lateral tibia. The trochlea was not segmented because of interfering flow artifacts from the popliteal artery. Interreader reproducibility errors of this technique were minimal, as reported in a prior study (36).

PA levels. PA was assessed in a consecutive sample of 2,127 consenting participants at the 48-month visit with a uniaxial accelerometer (ActiGraph GT1M) that measures vertical acceleration and deceleration and has been validated in several studies, showing a high correlation with metabolic equivalent and total energy expenditure, as well as with the ground reaction force as measured with a force plate (26,37). The reliability and accuracy of ActiGraph accelerometers have also been demonstrated in subjects with OA (38–40).

Participants were instructed to wear the accelerometer on a belt on the natural waistline for 7 consecutive days (26). PA was recorded through a weighted activity count, where the weights are proportional to the magnitude of measured acceleration. A valid day of monitoring required ≥10 wear hours in a 24-hour period. Nonwear periods were defined as ≥90 minutes of no activity counts (27). At least 4 valid days of monitoring were required to provide a reliable estimate of PA (26). Valid estimates were available for 1,927 activity substudy participants (91%).

For each of our 274 participants, the average daily time (minutes) spent with mv-PA, based on a threshold of >2,020 counts per minute, was calculated from the sum of daily total minutes of mv-PA divided by the number of valid days. We then stratified the subjects according to their activity levels (average daily minutes of mv-PA) into quartiles with the following ranges, lowest to highest in minutes: first = 0.6–10.2, second = 10.6–22.4, third = 22.8–38.9, and fourth = 39.6–133.9 (Table 1).

Statistical analysis. Statistical analysis was performed using SAS JMP software, version 11, and STATA software, version 12. In addition to descriptive statistics, chi-square tests were used to assess the differences in nominal variables such as sex, cohort, and OA risk factors between the PA groups. For continuous variables such as age and body mass index (BMI), differences between PA groups were determined using Kruskal-Wallis testing. Multivariate linear regression analysis was used to assess the associations of the predictor mv-PA quartiles with the outcome variables T2 relaxation time and WORMS (WORMS max and WORMS sum for menisci, cartilage, and BMEP). For each quartile, the adjusted mean ± SEM of the outcome variable is reported. *P* values represent significance of trends between the strata. For this test, the strata were treated as continuous scales in the model. Because of the relatively large number of comparisons made, we set the level of significance to *P* less than 0.01 (Table 2).

Covariates included in all analyses were age, sex, BMI, family history of knee-joint replacement, history of knee surgery, history of knee injury including injuries since the enrollment into the OAI study, and WOMAC pain, stiffness, and disability scores for left and right knees. We also included chronic

		mv-PA quartiles of average minutes/day, lowest to highest				
Table 1. Subject characteristics at 48-month visit*						
	All subjects (n = 274)	**First (n = 68)**	**Second (n = 69)**	**Third (n = 69)**	**Fourth (n = 68)**	***P***
Range of mv-PA, minutes	0.6–133.9	0.6–10.2	10.6–22.4	22.8–38.9	39.6–133.9	
Sex						< 0.001†
Men	134 (48.9)	28 (41.2)	23 (33.3)	35 (50.7)	48 (70.6)	
Women	140 (51.1)	40 (58.8)	46 (66.7)	34 (49.3)	20 (29.4)	
Cohort						0.691
Normal	2 (0.7)	0 (0)	1 (1.5)	1 (1.4)	0 (0)	
Incidence	253 (92.3)	64 (94.1)	64 (92.8)	61 (88.4)	64 (94.1)	
Progression	19 (6.9)	4 (5.9)	4 (5.8)	7 (10.1)	4 (5.9)	
K/L grade 1	81 (29.6)	20 (29.4)	22 (31.9)	17 (24.6)	22 (32.4)	0.744
Risk factors						
History of knee injury	57 (20.8)	11 (16.2)	12 (17.4)	17 (24.6)	17 (25.0)	0.352
Knee injury since baseline	9 (3.3)	1 (1.5)	3 (4.3)	2 (2.9)	3 (4.4)	0.740
History of knee surgery	13 (4.7)	1 (1.5)	4 (5.8)	3 (4.3)	5 (7.4)	0.409
Family history of knee replacement	47 (17.2)	8 (11.8)	10 (14.7)	7 (10.1)	22 (32.4)	0.002†
Heberden's nodes	67 (24.5)	13 (19.1)	19 (27.5)	20 (28.9)	15 (22.1)	0.560
Ipsilateral knee symptoms‡						
Pain	0.4 ± 0.8	0.5 ± 0.8	0.4 ± 0.9	0.4 ± 0.7	0.4 ± 1.1	0.937
Stiffness	0.4 ± 0.7	0.3 ± 0.6	0.4 ± 0.7	0.5 ± 0.8	0.5 ± 0.8	0.353
Functional limitation	0.7 ± 1.7	0.5 ± 1.3	0.8 ± 2.0	0.6 ± 1.7	0.7 ± 1.6	0.827
Contralateral knee symptoms‡						
Pain	0.3 ± 0.7	0.3 ± 0.7	0.4 ± 0.9	0.3 ± 0.6	0.3 ± 0.6	0.698
Stiffness	0.4 ± 0.7	0.4 ± 0.7	0.4 ± 0.7	0.4 ± 0.8	0.4 ± 0.7	0.923
Functional limitation	0.6 ± 1.6	0.6 ± 1.5	0.8 ± 2.2	0.5 ± 1.1	0.7 ± 1.4	0.787
Bilateral hip pain§	113 (41.2)	28 (41.2)	25 (36.2)	30 (43.5)	30 (44.1)	0.779
Bilateral ankle pain§	13 (4.7)	4 (5.9)	5 (7.3)	3 (4.3)	1 (1.5)	0.426
Age	59.1 ± 5.5	62.1 ± 5.5	58.3 ± 5.1	58.2 ± 6.0	57.8 ± 5.4	< 0.001†
BMI	26.8 ± 4.2	27.5 ± 4.4	27.1 ± 5.0	26.6 ± 3.9	25.8 ± 3.1	0.094

* Values are number (%) or mean ± SD unless indicated otherwise. mv-PA = moderate to vigorous physical activity; K/L = Kellgren/Lawrence; BMI = body mass index.
† Statistically significant at $P < 0.05$.
‡ Using categories from the Western Ontario and McMaster Universities Osteoarthritis Index.
§ Subjects who reported pain on either side at least 2 times since baseline.

hip pain and ankle pain to control for possible pain-induced alterations of the gait pattern that could have led to nonphysiologic loading of the right knee joint. Pain was defined as chronic if it was reported at least 2 times at the followup visits following baseline. We also adjusted for the mean daily wear time of the accelerometer (range 11–20 hours/day).

In addition, we analyzed the prevalence of structural knee lesions in relation to PA. For this purpose, WORMS lesions were dichotomized, counting lesions as present with WORMS grades >1 for cartilage and >0 for meniscus and BMEP. Significance of trends of prevalence and odds ratios was calculated using a multivariate logistic regression with the same covariates as described above.

RESULTS

Subject characteristics. Table 1 provides subject characteristics, including OA risk factors. Not surprisingly, participants in the highest quartile of mv-PA were more often men ($P < 0.001$) and were younger ($P < 0.001$) and had by trend a lower mean BMI ($P = 0.094$) than those in the lower activity levels. Men also had a higher frequency of family history of knee replacement ($P = 0.002$)

Level of PA and meniscus, cartilage, and BMEP lesions. Overall, more morphologic knee abnormalities were found with increasing levels of average daily minutes of mv-PA (Table 2 and Figure 2). Across all quartiles the subjects showed a significant gradual increase of the severity of meniscus lesions (WORMS max; $P = 0.0087$) and severity of BMEP lesions ($P = 0.0053$) and a significant increase in the total lesions in the menisci (WORMS sum; $P = 0.0089$) with increasing mv-PA. The association between the sum of meniscus lesions and PA quartiles was present only in the medial meniscus ($P = 0.0017$). There was also a nonsignificant trend for an increasing sum of BMEP lesions ($P = 0.0498$) by mv-PA quartile. There was no significant association between the severity or sum of cartilage lesions and quartiles of mv-PA. There were no differences by medial versus lateral compartments in the association of mv-PA with BMEP and cartilage lesions (data not shown). To exclude the possibility that the significant increase of meniscus lesions and BMEP with mv-PA was actually triggered by outliers of the fourth mv-PA quartile (showing the widest range of

Table 2. WORMS grades by quartile and T2 relaxation time*					
	mv-PA quartiles of average minutes/day, lowest to highest				
	First (n = 68)	**Second (n = 69)**	**Third (n = 69)**	**Fourth (n = 68)**	***P***
Meniscus					
WORMS max	1.43 ± 0.24	1.60 ± 0.22	1.78 ± 0.23	1.98 ± 0.22	0.0087†
WORMS sum	2.04 ± 0.53	2.70 ± 0.49	2.85 ± 0.51	3.31 ± 0.49	0.0089†
Sum of lesions, medial meniscus	1.19 ± 0.43	1.52 ± 0.41	1.76 ± 0.42	2.42 ± 0.40	0.0017†
Sum of lesions, lateral meniscus	0.84 ± 0.29	1.16 ± 0.28	1.09 ± 0.28	0.89 ± 0.27	0.9266
Cartilage					
WORMS max	3.10 ± 0.39	2.94 ± 0.32	3.08 ± 0.32	3.43 ± 0.31	0.2477
WORMS sum	5.9 ± 0.73	5.7 ± 0.68	5.5 ± 0.71	6.4 ± 0.67	0.5813
BMEP					
WORMS max	1.1 ± 0.20	1.0 ± 0.19	1.3 ± 0.19	1.5 ± 0.19	0.0053†
WORMS sum	1.6 ± 0.34	1.4 ± 0.32	2.1 ± 0.33	2.1 ± 0.31	0.0498‡
T2 (ms)					
LFC	35.8 ± 0.44	36.6 ± 0.42	36.4 ± 0.42	36.5 ± 0.39	0.1292
LT	29.5 ± 0.48	30.3 ± 0.44	30.2 ± 0.46	30.3 ± 0.43	0.131
MFC	38.1 ± 0.54	38.5 ± 0.51	38.9 ± 0.51	38.8 ± 0.48	0.102
MT	30.7 ± 0.43	31.7 ± 0.41	31.4 ± 0.42	31.8 ± 0.39	0.027‡
P	34.4 ± 0.6	35.0 ± 0.61	34.3 ± 0.62	35.1 ± 0.59	0.495
Average of all regions	33.8 ± 0.38	34.7 ± 0.35	34.4 ± 0.35	34.6 ± 0.32	0.054

* Least squares mean ± SEM, adjusted for age, sex, body mass index, family history of knee replacement, history of knee surgery or injury, Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, and disability (bilateral) hip and (bilateral) ankle pain, and average daily wear time of accelerometer. WORMS = Whole-Organ Magnetic Resonance Imaging Score; mv-PA = moderate to vigorous physical activity; WORMS max = highest score in any subcompartment; WORMS sum = sum of individual subcompartment scores; BMEP = bone marrow edema pattern; ms = milliseconds; LFC = lateral femoral condyle; LT = lateral tibia; MFC = medial femoral condyle; MT = medial tibia; P = patella.
† Statistically significant at $P < 0.01$.
‡ Trends ($P < 0.05$).

minutes/day [39.6–133.9]), we further stratified the highest quartile (n = 68) into subquartiles (n = 17). But when analyzing the highest subquartile (n = 17, range 70–133.9 minutes/day), we did not find a further increase of the sum of meniscus lesions (mean 3 compared to 3.3 for the entire fourth quartile) or sum of BMEP (mean 1.3 compared to 1.5 for the entire fourth quartile).

While the prevalence of all types of structural lesions was greatest in the highest mv-PA quartile, these findings were not significant. There was a nonsignificant trend for an increasing prevalence of medial meniscus lesions by mv-PA ($P = 0.031$) (Table 3).

Level of PA and cartilage T2 relaxation time. Overall, T2 values of the medial femoral condyle, the medial and lateral tibia, the patella, and the average joint cartilage tended to be greater in the higher quartiles of mv-PA, but the differences were relatively small and nonsignificant. A nonsignificant trend was found for T2 in the medial tibia ($P = 0.027$) (Table 2).

DISCUSSION

The results of this cross-sectional study show that middle-aged individuals without radiographic knee OA and with no or only mild symptoms, and who had higher mv-PA levels as measured by accelerometry, had increased severity of meniscal lesions, predominantly in the medial meniscus, and more severe BMEP lesions. We did not find an associa-

tion between the severity or prevalence of focal cartilage lesions and mv-PA. Moreover, no significant association was found between T2 relaxation time values in the cartilage indicative of cartilage matrix degradation and mv-PA.

The majority of studies investigating the role of occupational and community PA levels regarding the risk of development of knee OA in middle-aged adults and older have used self-report measures of PA and radiographic findings in the knee or total joint replacement. Findings from these studies have been conflicting (1,2,4–7,41). Recently, published longitudinal analyses of persons without knee OA at baseline from 3 large cohorts did not find a clear association between higher levels of general PA and the risk of developing knee OA (8,42). Felson et al performed analyses that combined data from the OAI and Multicenter Osteoarthritis cohorts, both of which used the Physical Activity Study in the Elderly (PASE) questionnaire, and found no association between higher levels of self-reported activity and the risk of developing symptomatic knee OA or joint space narrowing over 30–48 months (8). A study in the Johnston County cohort (42) used the Minnesota Leisure Time Activity Questionnaire and concluded that meeting the Health and Human Services PA guideline of ≥150 minutes per week of moderate or greater–equivalent activity was not associated with the incidence of radiographic or symptomatic knee OA. Notably, those participants who met the guidelines had a significantly increased risk of developing new joint space

WORMS lesions vs. physical activity quartiles
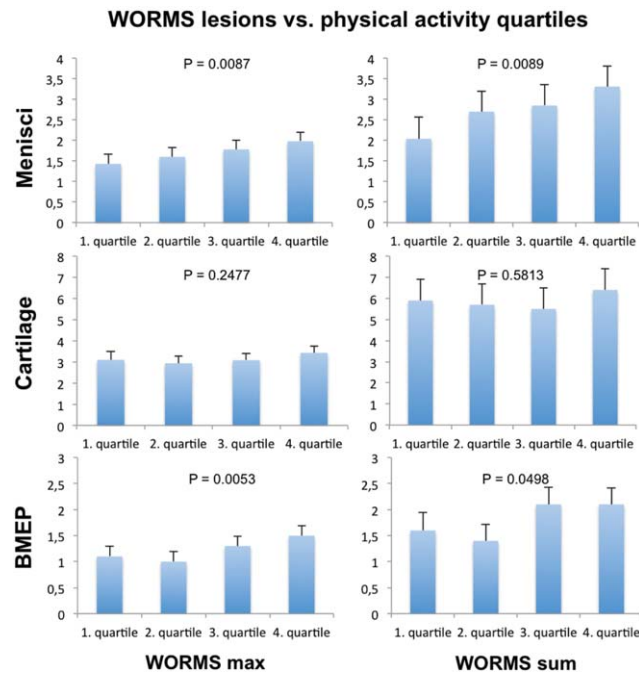
Figure 2. Least squares means of the Whole-Organ Magnetic Resonance Imaging Score (WORMS), for both maximum (WORMS max) and total of lesions (WORMS sum) of menisci, cartilage, and bone marrow edema pattern (BMEP). Bars on top of the columns show SE. Means are adjusted for age, sex, body mass index, family history of knee replacement, history of knee surgery or injury, Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, and disability (bilateral) hip and (bilateral) ankle pain, and average daily wear time of accelerometer.

narrowing, with adjusted hazard ratio 1.42 (95% confidence interval [95% CI] 1.10–1.82) and participants at the highest activity level (≥300 minutes/week of moderate or strenuous–equivalent activity) had a nearly significantly increased risk of incident radiographic knee OA (adjusted hazard ratio 1.62 [95% CI 0.97–2.68]) compared to the inactive group.

The insensitivity of radiographic findings to early OA and their inability to detect abnormalities in specific joint tissues, as well as the reporting bias induced by the self-

report of PA, may all contribute to these conflicting results. However, there are also disparate findings from studies using MRI to assess OA. In a study of healthy middle-aged individuals, self-report of vigorous PA was associated with greater tibial cartilage volume and fewer subchondral bone marrow lesions, suggesting a beneficial effect of greater activity on cartilage health (14). In contrast, our group previously reported that OAI subjects who were more active, in this instance assessed with the PASE questionnaire, had an increased prevalence of cartilage, meniscus, and ligamentous abnormalities, BMEP, and joint effusion on knee MRI as compared to less active subjects (16,17).

To our knowledge there has been only 1 other study that examined the relationship between objectively measured PA levels and MRI lesions in the knee (20), which had results that are consistent with ours. Doré et al (20) used a pedometer to identify persons averaging at least 10,000 steps per day, a threshold that has been promoted as a practical goal for achieving recommended PA levels (43), and found in a longitudinal analysis that these individuals had an increased risk of worsening meniscus damage and incident BMEP lesions. Consistent with our results, Doré et al did not find an increased risk of cartilage damage. Interestingly, these results were obtained using different objective methods for assessing physical activity. While pedometers are restricted to the measurement of step counts during walking or running, accelerometers provide a more general measure of PA that can be stratified into intensity levels and may include all types of PA that meet a certain intensity threshold. Classification of activity levels based on pedometers versus accelerometers can be widely divergent (44).

Higher T2 values are associated with risk factors for OA, including meniscal damage and malalignment (10,11,16), and predict progression of cartilage morphologic lesions (45). Therefore, assuming that increased PA constitutes a risk factor for cartilage degeneration, higher cartilage T2 values could be expected with increasing PA. However, in the present study, we did not find a significant association between higher objectively assessed PA and T2 values. These results are somewhat in contrast to our prior analy-

Table 3. Prevalence of dichotomized WORMS findings by quartile of any grade*						
	Average daily minutes of moderate to vigorous physical activity, lowest to highest					
	First (n = 68)	**Second (n = 69)**	**Third (n = 69)**	**Fourth (n = 68)**	**OR (95% CI)**	**P†**
WORMS meniscus lesions	38 (55.9)	37 (53.6)	41 (59.4)	47 (69.1)	2.01 (0.85–4.83)	0.098
WORMS medial meniscus lesions	29 (42.7)	26 (37.7)	29 (42.0)	41 (60.3)	2.45 (1.09–5.64)	0.031‡
WORMS lateral meniscus lesions	21 (30.9)	23 (33.3)	28 (40.6)	24 (35.3)	1.19 (0.51–2.81)	0.584
WORMS cartilage lesions >grade 1	56 (82.4)	58 (84.1)	60 (86.9)	65 (95.6)	1.68 (0.65–4.49)	0.275
WORMS BMEP	46 (67.7)	41 (59.4)	46 (66.7)	49 (72.1)	1.90 (0.81–4.53)	0.071

* Values are number (%) unless indicated otherwise. WORMS = Whole-Organ Magnetic Resonance Imaging Score; OR = odds ratio; 95% CI = 95% confidence interval; BMEP = bone marrow edema pattern.
† Significance of trend ($P < 0.01$) was tested with logistic regression; covariates included age, sex, body mass index, family history of knee replacement, history of knee surgery or injury, Western Ontario and McMaster Universities Osteoarthritis Index pain, stiffness, and disability (bilateral) hip and (bilateral) ankle pain, and average daily wear time of accelerometer.
‡ Trends ($P < 0.05$).

ses of OAI subjects that found individuals in the highest PA group, based on the PASE questionnaire, had higher T2 values in several knee cartilage regions in cross-sectional analyses, compared to those in the middle-activity level or compared to all lower-activity levels (16,18). This discrepancy is, however, not unexpected when comparing PASE data and data derived from accelerometers. While subjective questionnaires count frequencies of specific types of PA, accelerometers objectively measure intensity, frequency, and volume of general PA.

Viewing our findings in a pathophysiologic context, probably the weakest structure according to sustained mechanical load during mv-PA is the medial meniscus, while cartilage seems to be relatively resilient towards increased PA. The trend for higher T2 values in the cartilage of the medial tibia indicates a stress-associated early cartilage degradation and is consistent with the presence of more severe lesions of the medial meniscus (11). In OA, BMEP lesions are associated with increasing severity of cartilage lesions (46). In this context, BMEP lesions were more severe in the most active subjects, although the severity of cartilage lesions was comparable among the PA strata. One explanation may be that cartilage with preexisting lesions, which were very common at all activity levels in the study knees, is insufficient in absorbing mechanical load, thus transmitting axial forces more directly to the subchondral bone. As a consequence, increased loading may lead to a higher mechanical stress of the subchondral bone, resulting in more severe BMEPs.

Our findings that increasing levels of PA are associated with increases in the severity of meniscus and subchondral bone lesions, however, have to be interpreted with caution. Most importantly, whether these preradiographic MRI findings confer an increased risk of eventually developing clinically manifest knee OA is uncertain. While there is clear evidence that total and to a lesser extent partial meniscectomy leads to a significantly higher risk in developing OA, there is still a scarcity of data about the role of prevalent meniscal lesions for the development of OA. A study in the Multicenter Osteoarthritis Study cohort comparing 121 cases who developed radiographic OA after 30 months with 294 controls found an 8-to-10–fold increased risk for the development of knee OA associated with the presence of meniscal tears, suggesting that these lesions are an important structural risk factor for the development of OA (47). Also the presence of BMEP lesions was predictive for local structural degeneration of the knee joint in a study by Felson et al, who reported a 6-fold increased risk for the progression of radiographic OA (48) and for cartilage loss in MRI as reported by Hunter et al (49). Nevertheless, greater levels of PA possibly have both beneficial and detrimental effects on knee-joint health; whether one or the other predominates in the long run can only be determined from longitudinal studies with clinically relevant end points.

Only a small proportion of people in OAI and other studies using objective measures actually meet current recommendations for PA (42,43), and public health efforts encouraging greater achievement of these goals are under way. Although our findings indicate that higher PA may be considered as a risk factor for knee OA, this finding may not necessarily account for all subjects meeting current PA guidelines (50). PA at the level recommended by these guidelines is by most standards relatively modest and has been linked to a variety of important health benefits; potential effects of activity at these levels on knee-joint health need to be balanced against the known benefits. For this reason we wanted to exclude the possibility that the significant increase of meniscus lesions and BMEP with mv-PA was actually triggered by outliers who performed mv-PA more than 70 minutes per day, but no further increase of lesions in this high-performing subgroup was found.

Our study has several key strengths. This study is 1 of only 2 that have evaluated the association between PA and OA with objectively measured physical activity. We used knee MRI, which is sensitive to early abnormalities of OA. We selected subjects with risk factors for the development of OA but without radiographic OA and with no or only mild knee symptoms. Moreover, we tried to avoid a potential bias by excluding persons with knee pain who might have adapted their PA as a result of pain. Therefore, the characteristics of the study cohort are uniquely optimized to detect early degenerative changes in response to PA. However, the finding of asymptomatic subjects with meniscus lesions and BMEPs may also indicate that these subjects were actually tolerating their lesions well, and it finally remains unclear whether the PA in these patients has to be counted only as a risk factor or also as a beneficial factor that helps the patients to cope with their knee pain. Moreover, this selection may not allow us to generalize our results with regard to healthy individuals without risk factors or to subjects who already have knee OA or severe knee pain, thus explaining some of the discrepancy of our results compared to other studies, as described above. Therefore these results need to be confirmed in a broader cohort, including all stages of OA.

There are additional limitations of our study. First, we made a large number of separate comparisons and some of the associations may represent chance findings. For this reason we set the level of significance to $P < 0.01$. Second, the associations between PA and OA that we found were probably not caused by current activity but rather by activity undertaken in the past and at younger ages in those who are still more active. However, measuring PA with an accelerometer can only cover a limited time period and may not allow extrapolating activity levels to longer intervals. Third, while accelerometer data measure intensity and duration of PA, they do not identify specific exercise or occupational activities that are more likely to result in joint tissue damage. Finally, our study was cross-sectional, precluding any inference about causation. Further longitudinal studies are needed to investigate whether higher PA leads to an acceleration of knee-joint degeneration and which particular types of exercise are more likely to cause joint damage with higher PA levels.

In summary, we found that in knees of subjects with no to mild OA symptoms and without radiographic OA, high levels of PA as measured by accelerometer were associated with an increased severity of meniscal and BMEP lesions, while cartilage showed no increase of damage in response to PA. The implications of these findings for long-term health of the knee in active individuals remain to be determined.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Kretzschmar 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.

Study conception and design. Kretzschmar, Lin, Nardo, Heilmeier, Nevitt, Alizai, McCulloch, Lynch, Link.

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Analysis and interpretation of data. Kretzschmar, Lin, Nardo, Joseph, Dunlop, Heilmeier, Nevitt, McCulloch, Link.

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