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Brief Report

Physical activity is associated with changes in knee cartilage microstructure

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SUMMARY

Objective: The purpose of this study was to determine if there is an association between objectively measured physical activity and longitudinal changes in knee cartilage microstructure.
Methods: We used accelerometry and T_2-weighted magnetic resonance imaging (MRI) data from the Osteoarthritis Initiative, restricting the analysis to men aged 45–60 years, with a body mass index (BMI) of 25–27 kg/m^2 and no radiographic evidence of knee osteoarthritis. After computing 4-year changes in mean T_2 relaxation time for six femoral cartilage regions and mean daily times spent in the sedentary, light, moderate, and vigorous activity ranges, we performed canonical correlation analysis (CCA) to find a linear combination of times spent in different activity intensity ranges (Activity Index) that was maximally correlated with a linear combination of regional changes in cartilage microstructure (Cartilage Microstructure Index). We used leave-one-out pre-validation to test the robustness of the model on new data.
Results: Nineteen subjects satisfied the inclusion criteria. CCA identified an Activity Index and a Cartilage Microstructure Index that were significantly correlated ($r = .82$, $P < .0001$ on test data). Higher levels of sedentary time and vigorous activity were associated with greater medial-lateral differences in longitudinal T_2 changes, whereas light activity was associated with smaller differences.
Conclusions: Physical activity is better associated with an index that contrasts microstructural changes in different cartilage regions than it is with univariate or cumulative changes, likely because this index separates the effect of activity, which is greater in the medial loadbearing region, from that of patient-specific natural aging.

Introduction

Physical activity is a known antidote to many health conditions, but given the intrinsic relationship between mechanical loading and cartilage metabolism, its effect on the structural progression of knee osteoarthritis (OA) is not well understood. Excessive cyclic loading is now accepted as an important factor in the etiology of OA. At the same time, loading is necessary for healthy cartilage homeostasis. It is thus reasonable to hypothesize that there exists an optimal range of physical activity that can preserve healthy cartilage metabolism and hamper OA. Finding this optimal range would enable the development of effective activity-modification interventions to protect the knee joint.

The literature on how physical activity relates to cartilage composition is sparse, and the results are not always in agreement. Several studies have reported that activity is associated with an increased risk of radiographic knee OA or Magnetic Resonance Imaging (MRI) features indicative of early OA[1–7]. Others have reported either no association[8] or opposite findings[9]. One factor that may contribute to conflicting findings is cartilage responding to activity differently across the population. Additionally, most previous studies were limited by the following: (1) lack of longitudinal MRI data, (2) representation of physical activity as one score with

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no characterization of different intensities and durations, (3) univariate statistical analyses, (4) reliance on self-reported assessments of activity and semi-quantitative scores of cartilage structure.

Wearable sensors and T_2-weighted MRI allow objective and granular representations of activity and cartilage microstructure, which can lead to deeper insights on how the two are interrelated. The purpose of this study was to determine if physical activity is associated with longitudinal changes in knee cartilage microstructure in a cohort of men with similar characteristics. We used objective physical-activity data from belt-worn accelerometers and T_2-weighted MR images of cartilage microstructure acquired at two different time points. We hypothesized that physical activity is significantly associated with longitudinal changes in cartilage microstructure and that light, moderate, and vigorous activities contribute differently to these changes. To overcome the burden of multiple hypothesis testing, we incorporated the multitude of features representing physical activity and cartilage microstructure in a single multivariate model.

Methods

Subjects

We used activity monitoring and knee MRI data from the Osteoarthritis Initiative, a longitudinal observational study of the natural progression of knee OA (https://oai.epi-ucsf.org/). As part of this study, subjects had their right knees scanned yearly and participated in a 1-week activity-monitoring study at the fourth year. To remove the potential effect of confounders, we restricted this analysis to men aged 45–60 years, with a body mass index (BMI) of 25–27 kg/m^2 and no radiographic evidence of OA during the first 4 years of the study (Kellgren Lawrence grade ≤ 1). Twenty subjects satisfied these inclusion criteria, but one was excluded due to motion artifact in one of the image volumes. Although the included subjects did not have OA, they were at risk of developing it due to risk factors that were part of the OAI inclusion criteria (e.g., pain, family history, previous knee injury, occupational burden).

Physical activity

Physical activity was measured using a belt-worn uniaxial accelerometer (ActiGraph, LLC, Pensacola, FL) and data were provided in activity counts per minute[10]. An activity count is a weighted sum of the number of vertical movements, where the weights are proportional to the magnitude of the measured acceleration. Participants wore the accelerometer for 7 consecutive days, and data were considered valid if at least 10 h of wear time per day were available. Subjects with fewer than 4 valid days were excluded from the study. We binned the accelerometry data into four intensity ranges that correspond to sedentary time (0–100 counts), light (101–573 counts), moderate (574–4944 counts), and vigorous (4945 + counts) activity. These thresholds are based on energy-expenditure estimates validated in an older adult population[11]. We averaged the number of daily minutes spent in each intensity range across the weekdays.

Knee imaging

To determine longitudinal changes in cartilage microstructure, we assessed baseline and year four follow-up MRI scans. Imaging was performed at one of four OAI sites, which used identical 3.0 T scanners (Siemens, Erlangen, Germany). We used the sagittal 3-D dual echo in the steady state images (echo time = 4.7 ms, repetition time = 16.3 ms, resolution 0.365 mm × 0.456 mm × 0.7 mm, flip angle 25°) to segment the right knee femoral cartilage. Segmentations were performed using an atlas-based method[12] (Qmetrics Technologies, Rochester, NY), inspected by an expert musculoskeletal radiologist, and then co-registered with the T_2-weighted images. We used sagittal T_2-weighted multi-echo spin-echo images (repetition time = 2700 ms, echo times = 10, 20, 30, 40, 50, 60, 70 ms, resolution = 0.313 mm × 0.446 mm × 3 mm) to generate T_2 maps using a nonlinear minimization fit: $S_{TE} = S_0 \exp(-TE/T_2)$, where TE is the echo time, S_{TE} is the measured signal intensity, and S_0 is the apparent proton density. Mean T_2 relaxation times were computed for the whole cartilage, as well as six regions of interest: the medial posterior, medial loadbearing, medial trochlea, lateral trochlea, lateral loadbearing, and lateral posterior. These regions were selected using a previously validated atlas-based method[12] and inspected by an expert radiologist. Knee alignments had been previously computed from fixed-flexion X-rays taken at the baseline visit[13].

Statistical analysis

We used canonical correlation analysis (CCA) to determine if there was an association between physical activity and longitudinal changes in cartilage microstructure. CCA is a multivariate extension of correlation analysis that finds linear relationships between two sets of multivariate vectors, $X = (x_1, \ldots, x_n)$ and $Y = (y_1, \ldots, y_m)$, representing measurements taken from the same subjects. The analysis finds a set of vectors a and b that maximize $corr(a^TX, b^TY)$, where a^TX and b^TY are the first canonical variates. Here, we call them the Activity and Cartilage Microstructure Indices.

To determine the most consequential types of activities and the most affected cartilage regions, we computed correlations among the original variables (e.g., time spent in the vigorous range) and the respective canonical variate (e.g., Activity Index). The errors associated with the CCA coefficients were computed using a bootstrapping procedure (1000 samples). To determine the statistical significance of the CCA, we used a permutations test (1000 permutations). Additionally, we performed leave-one-out pre-validation[14], carrying out the CCA with 18 subjects and using the derived model to determine the Activity and Cartilage Microstructure Indices for the left-out subject. We repeated this procedure 19 times and report the Pearson correlation coefficient here.

Results

At the baseline visit, subjects had a mean (±SD) age of 52 ± 4 years, BMI of 25.9 ± 1.2 kg/m^2, and knee alignment angle of −6.4 ± 1.6°, which is indicative of varus malalignment[13]. The mean (±SD) amounts of daily time spent in the sedentary, light, moderate, and vigorous ranges were 729 ± 92, 177 ± 44, 164 ± 63, and 4 ± 5 min, respectively. The mean (±SD) change in average T_2 relaxation time over the course of 4 years was 2.3 ± 3.6 ms for the whole cartilage.

CCA identified an Activity Index and a Cartilage Microstructure Index that were significantly correlated ($r = .96$, $P = .0040$; Fig. 1(A)). The other canonical variates were not significantly correlated. The performance of the model on left out data indicated that physical activity can be used to predict changes in cartilage microstructure with high accuracy (pre-validation Pearson's $r = 0.82$, $P < .0001$; Fig. 1(B)). The Activity Index contrasted sedentary time and vigorous activity with light activity [Fig. 2(A)]. Sedentary time and vigorous activity were positively correlated with the Activity Index (variable-variate Pearson's $r = .81$, $P < .0001$ for sedentary and $r = .76$, $P = .0002$ for vigorous; Fig. 2(C)), whereas high levels of light activity were negatively correlated ($r = -.77$, $P = .0001$). Moderate activity showed a weaker association with the

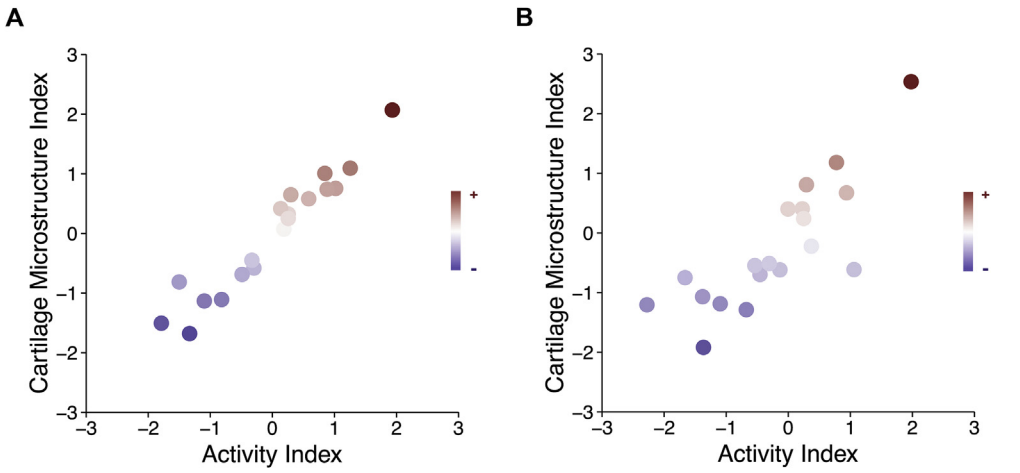

Fig. 1. The Association of Physical Activity with Cartilage Microstructure. (A) The Activity Index and Cartilage Microstructure Index identified through canonical correlation analysis (CCA) were significantly correlated ($r = .96$; $P = .0040$). An increasing Activity Index is indicative of more time spent in the sedentary and vigorous activity bins and less time in the moderate activity bin, whereas an increasing Cartilage Microstructure Index is indicative of greater differences between T_2 changes in the medial and lateral compartments. (B) Pre-validation using a leave-one-out schema indicated that in new subjects, not included in the model building, the Activity Index and Cartilage Microstructure Index were also highly correlated (Pearson's $r = .82$, $P < .0001$). Redder points indicate a more positive, whereas bluer points indicate a more negative, Cartilage Microstructure Index.

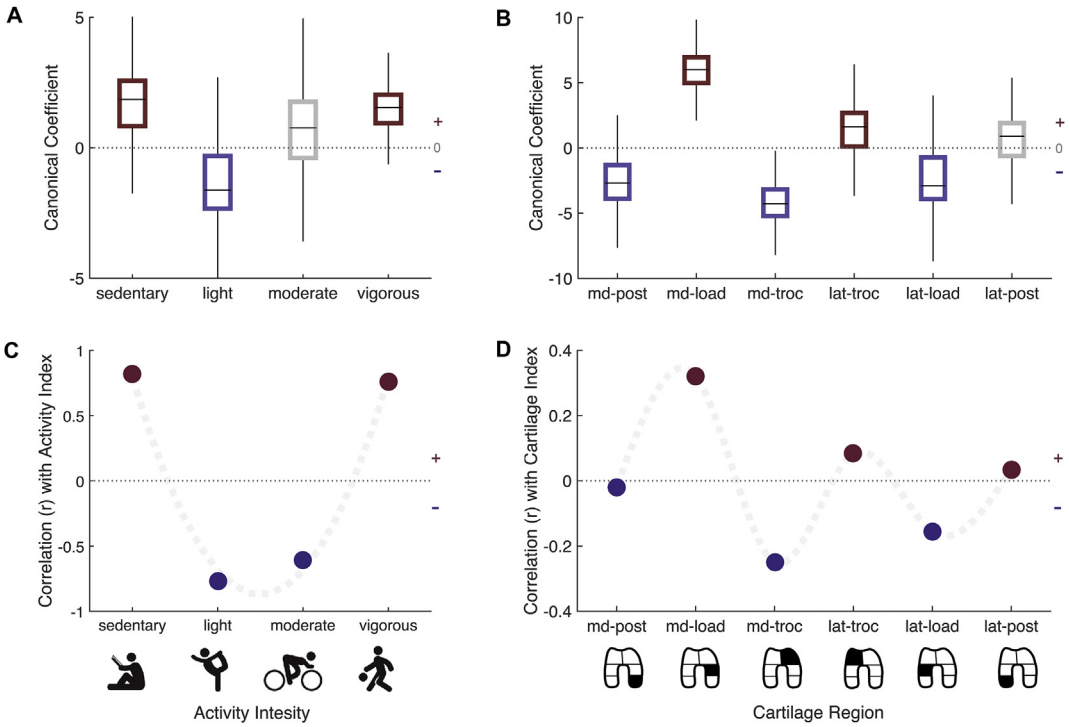

Fig. 2. Interpretation of the Activity and Cartilage Microstructure Indices. Canonical coefficients indicate that (A) the Activity Index contrasts the amounts of time spent in the sedentary and vigorous activity ranges with that spent in the light range. (B) The Cartilage Microstructure Index contrasts T_2 changes in adjacent regions of the femoral cartilage. Red indicates positive coefficients and blue indicates negative coefficients. Boxes (median, 25 and 75 percentiles) and whiskers (all the data points not considered outliers) show the errors associated with each coefficient, which were estimated using a bootstrapping procedure. Correlations among the original variables and the respective canonical variates indicate that (C) times spent in the sedentary and vigorous activity ranges are positively correlated with the Activity Index, whereas times spent in the light and moderate ranges are negatively associated with the Activity Index (dashed gray function is plotted for illustrates purposes only). (D) T_2 changes in specific cartilage regions were not significantly correlated with the Cartilage Microstructure Index, but the contrast between medial and lateral loadbearing regions was (dashed gray function is plotted for illustrates purposes only).

Activity Index ($r = -.61$, $P = .0056$). Correlations of activity types with the Cartilage Microstructure Index were similar (i.e., differences in r values less than .03). The Cartilage Microstructure Index contrasted T_2 changes in adjacent cartilage regions [Fig. 2(B)]. A more positive Cartilage Microstructure Index was indicative of greater differences between the medial and lateral compartments (e.g., 3.9 ± 3.4 ms vs 0.9 ± 3.3 ms in the loadbearing region), whereas a negative index was indicative of smaller differences between the compartments (e.g., 2.1 ± 4.7 ms vs 1.2 ± 3.7 ms in the loadbearing region). The individual T_2 changes in different cartilage regions were not correlated with the Cartilage Microstructure Index ($|r| < .32$, $P > .1804$; Fig. 2(D)), but the contrast between the medial and lateral loadbearing regions was positively correlated ($r = .70$, $P = .0008$). Correlations of regional T_2 changes with the

Activity Index were similar (i.e., differences in r values less than .01).

Discussion

Exercise is hailed for its potential to improve function and mitigate pain in arthritic patients. Yet, the current understanding of how different types and doses of activity affect cartilage composition is fractured, hindering the design of effective activity-modification interventions. A key challenge is that both physical activity and cartilage microstructure data are multi-dimensional; thus, traditional statistical tools cannot efficiently model the relationship between the two. This study provides evidence that a multivariate analysis can take advantage of the covariance in the data to identify weak associations that together create a significant effect, generating new insights even with a small cohort.

In our cohort, we did not observe significant associations between physical activity and regional changes in cartilage microstructure (bivariate correlation results not presented here). Instead, an index that contrasts changes in different regions was more informative. This finding may be explained by the fact that cartilage microstructure changes differently across the population due to a multitude of known and unknown confounders. The subjects included here had varus malalignment, indicating that their medial compartment is continuously loaded more than the lateral. Thus, a measurement that contrasts microstructural changes in adjacent regions of the joint would be better associated with physical activity than one that considers cumulative or regional changes alone.

Our finding that sedentary behavior and vigorous activity may be unsafe for individuals at risk for knee OA is consistent with previous thoughts and findings. A previous study that classified 205 subjects based on cumulative scores from the Physical Activity Scale for the Elderly questionnaire found that those in the lowest and highest activity quartiles exhibited greater 4-year changes in cartilage microstructure[3]. With a multivariate analysis, we were able to draw similar conclusions using a smaller cohort. Additionally, our approach provided insight into how specific intensities and durations of activities relate to cartilage heath.

When interpreting our findings, the following characteristics of the study should be taken into consideration. First, there may be other covariates—in addition to sex, age, BMI, and OA status—that interact with physical activity. Given the small number of subjects, we focused only on a few commonly reported confounders. Second, activity was measured over the course of 1 week, which may not be representative of general habits. Even though a limitation, we believe that activity monitoring with wearable devices is an improvement over the use of questionnaires. Third, to bin the activity data, we used thresholds from previous experiments[11], which may not generalize well to new populations. Fourth, although we found an association between physical activity and longitudinal changes in cartilage microstructure, a cause-and-effect relationship cannot be established given our study design. Last, our study characterizes longitudinal changes in T_2 relaxation time, rather than short-term, transient changes measured immediately after exercise, which have been the focus of other studies[15].

In this study we have shown that it is possible to identify ranges of activity intensity and duration that are associated with better cartilage health. Learning how these ranges vary across individuals with different characteristics has the potential to boost OA prevention efforts significantly. With the expansion of wearable technology, refinement of MRI sequences, and growing permeation of data science into the biomedical realm, the design of personalized activity-modification interventions informed by accurate predictive models now appears feasible.

Author contributions

All authors made substantial contributions to the conception and design of the study, data analysis and interpretation, drafting the article or critical revision for important intellectual content, and final approval of the submitted version.

Competing interest statement

None of the authors have financial or personal relationships that could potentially influence the conclusions of this work.

Role of the funding source

The contents of this work are the responsibility of the authors and do not represent the official views of the NIH.

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