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Multivariate functional principal component analysis identifies waveform features of gait biomechanics related to early-to-moderate hip osteoarthritis.

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Abstract

Clinicians often examine movement patterns to design hip OA interventions, yet traditional biomechanical analyses only report a single timepoint. Multivariate principal component analysis (MFPCA) analyzes the entire waveform (i.e., movement pattern), which clinicians observe to direct treatment. This study investigated hip OA indicators, by 1) employing MFPCA to characterize variance across hip, knee, and ankle angles in healthy and early-to-moderate hip OA participants; and 2) investigating relationships between these waveform features and hip cartilage health. Bilateral hip magnetic resonance images from 72 participants with Kellgren-Lawrence grades ranging from 0–3 were used to calculate mean $T_{1\rho}$ and T_2 relaxation times in the femoral and acetabular cartilage. MFPCA was performed on lower-limb gait biomechanics and used to identify primary modes of variation, which were related to $T_{1\rho}$ and T_2 relaxation times. Here, a MFPC = mode of variation = waveform feature. In the femoral cartilage, transverse plane MFPCs 3 and 5 and BMI were related to $T_{1\rho}$, while MFPC 2 and BMI were related to T_2 relaxation times. In the acetabular cartilage, sagittal plane MFPC 1 and BMI were related to $T_{1\rho}$, while BMI was related to T_2 relaxation times. Greater internal rotation was related to increased $T_{1\rho}$ and T_2 relaxation times in the femoral cartilage, while greater extension was related to increased $T_{1\rho}$ relaxation times in the acetabular cartilage. This study established a data-driven framework to assess relationships between multi-joint biomechanics and quantitative assessments of cartilage health and identified waveform features that could be evaluated in future hip OA intervention studies.

Keywords

hip osteoarthritis; multivariate functional principal component analysis; magnetic resonance imaging; $T_{1\rho}$ and T_2 relaxation times; gait biomechanics

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1 INTRODUCTION

Arthritis is the primary cause of disability in the US,[1] incurring approximately $81 billion in direct medical costs each year.[2] Osteoarthritis (OA), the most common form of arthritis, is characterized by degeneration of the tissues in the afflicted joint and can cause joint pain, limited range of motion, and decreased quality of life. OA is more prevalent in weight bearing joints, with hip OA alone reported to afflict up to 27% of US adults over the age of 45.[3] Early detection mechanisms and preventative techniques are necessary to decrease the number of individuals afflicted by painful, end-stage hip OA and the associated financial burden incurred as a result.

Little information exists regarding effective methods to prevent hip OA or treatments for early-stage hip OA. Age, sex, and body mass index (BMI) have been associated with hip OA[4; 5] and could be considered risk factors for the disease. Although the results of BMI modification through weight-loss interventional studies are promising,[6; 7] these studies were only in the knee and do not include quantitative evaluations of cartilage health. Furthermore, some individuals in the healthy BMI range, including younger individuals and athletes, such as those with femoroacetabular impingement, have a higher risk for developing hip OA.[8] These younger individuals need an effective biomarker, independent of BMI, to portend the risk or onset of early-stage hip OA, so that preventative measures can be implemented.

Besides demographics, altered hip joint loading patterns have been clinically hypothesized to contribute to hip OA.[9] Although studies have found gait biomechanics (i.e., joint kinematics and kinetics) changes in participants with end-stage hip OA,[10] these results could be attributed to pain[11] or decreased muscle strength.[12] However, participants with early-to-moderate hip OA may exhibit altered gait biomechanics that are already detectable and less influenced by lower-limb pain and/or strength changes. Previous studies[13; 14] demonstrated a variety of results, which can make it difficult to ascertain which biomechanical gait characteristics are indicative of early-stage hip OA. Additionally, these biomechanical analyses were limited to averaged or singular data points (e.g., peak hip flexion or foot-strike), which limits the applicability of these results to clinical interventions, as clinicians would need to observe the entire waveform in order to direct a treatment. In order to modify gait and investigate the ability of these modifications to prevent or treat early-stage hip OA, waveform features will need to be identified and associated with cartilage degeneration.

Studies have demonstrated that biochemical changes in articular cartilage coincide with or precede the development of OA,[15–17] which can be quantitatively measured with magnetic resonance (MR) $T_{1\rho}$ and T_2 relaxation times. In cartilage, $T_{1\rho}$ is an indicator of proteoglycan content, with higher $T_{1\rho}$ relaxation times corresponding to decreased proteoglycan content.[18] T_2 is an indicator of water content and collagen organization, with higher T_2 relaxation times corresponding to increased water content and disorganization of the cartilage.[19] Accordingly, increases in $T_{1\rho}$ and T_2 relaxation times are linked to cartilage degeneration and may detect cartilage degradation earlier than traditional OA radiologic scoring systems.[20; 21]

Functional data analysis is a statistical technique used to analyze data that exists over a smooth continuum, wherein each point is related to the next along the continuum (e.g., gait biomechanics kinematic data). Multivariate functional principal component analysis (MFPCA), is a multi-modal technique built upon the fundamentals of functional data analysis that can concurrently analyze variance across different domains and associations between these domains. MFPCA is not affected by dimensionality, reducing the need for additional pre-processing, normalization, or other manipulations prior to analysis.[22] To investigate hip OA indicators aside from BMI, we 1) employed MFPCA to characterize variance across hip, knee, and ankle angles in healthy and early-to-moderate hip OA participants; and 2) investigated relationships between these waveform features and hip cartilage health.

2 METHODS

2.1 Study Participants

This was a cross-sectional study involving human participants (Level of Evidence: III). Following approval by the institutional Committee on Human Research, healthy volunteers and those with varying degrees of hip OA were recruited and provided written informed consent prior to participation in this study. Participation in this study was contingent upon having no hip OA or mild-to-moderate hip OA (Kellgren-Lawrence grade 0–3). Bilateral hip anterior-posterior and lateral screening radiographs were obtained of each participant. All radiographs were reviewed and the Kellgren-Lawrence (KL) grade[21] determined by a fellowship-trained radiologist. Exclusion criteria for all participants included those under the age of 18, prior history of hip surgery, any presence of knee OA and an affirmative response to all NHANES survey questions, hip trauma within the previous three months, intra-articular injection within the last 6 months, inflammatory arthropathy, hematochromatosis, sickle cell disease, hemoglobinopathy, immobility or assistance requirements which affect motion analysis, or contraindications to MRI. Participants were excluded from the current study if they had an alpha angle greater than 55° and a positive flexion, adduction, and internal rotation (FADIR) exam.

2.2 Magnetic Resonance Image Acquisition and Analysis

Bilateral hip MR images (Table 1) were acquired of each participant on a three Tesla MR scanner (GE Healthcare, Waukesha, WI) with a 32-channel coil (GE Healthcare, Waukesha, WI). The toes of each participant were secured in place to stabilize the lower limbs and create an anatomical neutral during the scan. Coronal T_2 and 3D fast spin echo (FSE) Cube sequences with sagittal, axial and oblique axial reconstructions were used for morphological evaluation of the acetabular and femoral cartilage using the Scoring Hip OA with MRI (SHOMRI) grading system as previously described[23]. A sagittally combined $T_{1\rho}/T_2$ Magnetization-Prepared Angle-Modulated Partitioned k-Space Spoiled Gradient Echo Snapshots (MAPSS) sequence was acquired of each hip. The $T_{1\rho}$ preparation pulses contained continuous hard tip down pulses ($90°_x$) followed by a hard, opposite phase 135° pulse and a spin lock tip up pulse ($90°_{-x}$). The T_2 preparation pulse included of a Malcolm Levitt's composite pulse decoupling sequence consisting of $90°_x 180°_y 90°_x$ nonselective composite refocusing pulses, where pulse duration was 1.624 ms.[24] A single atlas-based

registration technique was used to segment the femoral and acetabular cartilage volumes.[25] Briefly, the reference atlas was chosen as the participant images that minimized the average deformation when transformed. The first spin lock time (TSL) = 0ms $T_{1\rho}$-weighted image of each participant was non-rigidly registered to the reference atlas. This transformation field was then applied to the remaining TSLs for that participant, which aligned the $T_{1\rho}$-weighted images of each participant to the reference atlas.[25] A Levenberg-Marquardt monoexponential $\left(S(TSL) \propto e^{\frac{-TSL}{T1\rho}}\right)$ was applied to each voxel of the $T_{1\rho}$-weighted images of each TSL to create $T_{1\rho}$ maps of each participant. This process was repeated using echo times (TEs) to create T_2 maps.[24] The femoral and acetabular cartilage masks from the reference atlas were applied to the morphed $T_{1\rho}$ and T_2 maps of each participant. The mean $T_{1\rho}$ and T_2 relaxation times were calculated across each cartilage volume.[25]

2.3 Skin Marker Data Acquisition and Analysis

Retroreflective skin markers were placed on each participant prior to biomechanical data acquisition. Skin markers were placed on the iliac crests, anterior superior iliac spines, posterior superior iliac spines, L5/S1 joint, and bilateral greater trochanters, medial and lateral femoral epicondyles, medial and lateral malleoli, and heads of the first and fifth metatarsals. Skin marker clusters were attached to the bilateral thigh, shank, and heel counter of each shoe of each participant.[26; 27]

Three-dimensional (3D) skin marker trajectory data was acquired at 250Hz using a 10 camera near-infrared system (Vicon Nexus, Oxford Metrics LTD., Oxford, UK). Ground reaction forces were simultaneously acquired at 1000 Hz from two in-ground force plates (AMTI, Watertown, MA). Participants performed a standing calibration trial and walked across two in-ground force plates along a 10-meter walkway at 1.35 m/s. A successful trial was defined as a trial in which the entire foot strike fell entirely on one force plate. Participants completed a minimum of five successful walking trials for each leg.

The trajectory and ground reaction force data were filtered with a fourth order, zero lag, low-pass Butterworth filter with cutoff frequencies of 6 Hz and 50 Hz, respectively (Visual3D, C-Motion, Germantown, MD). Ground reaction force data was used to automatically detect foot-strike and foot-off for each trial and thereby determine stance phase. Bilateral hip, knee, and ankle joint angles were calculated with a medial-lateral, anterior-posterior, superior-inferior (XYZ) Cardan sequence and normalized to stance phase (Visual3D).

2.4 Statistical Analysis

To prevent the wash out of any key waveform features, one representative trial of each participant was randomly chosen and analyzed.[28] The MFPC and stepwise linear regression analyses were performed in the R environment for statistical computing (R Development Core Team, v3.3.3) using the fda, funData, MFPCA, lmtest, and MASS packages. First, each joint angle curve was fit to a mathematical function. Next, the mathematical functions representing the hip, knee, and ankle angles of the participants were combined in each plane. Three MFPCAs were performed on this combined data, one in each plane.[2922] Each MFPCA identified 10 MFPC modes of variation for a total of 30 MFPC modes, where

each MFPC or mode of variation described a waveform feature. The combined hip, knee, and ankle angle mathematical functions of each participant were assigned an MFPC score for each mode of variation. The MFPC score represents how much of a given waveform feature (mode of variation) a participant has relative to the other participants. For example, participants with a high MFPC score had combined joint angles with more of the described waveform feature. For each plane, a screeplot of the change in variance explained by each MFPC was used to qualitatively estimate the point of diminishing returns and the number of MFPCs to include in each regression model.

A stepwise linear regression model was used to relate the demographic features and MFPCs to the mean acetabular and femoral cartilage $T_{1\rho}$ and T_2 relaxation times. First, regression models employed only age, sex, and BMI as independent variables. Next, MFPCs were incorporated into the models as independent variables, along with the significant demographic variables, and compared to the initial regression models. Mean acetabular and femoral $T_{1\rho}$ and T_2 relaxation times were outcome variables for the regression models. A forward and backward stepwise search mode and a penalty equal to 3.8 multiples of the degrees of freedom were used to select regression models. Independent variables were included in the final regression models if the incorporation of these variables decreased the Akaike information criterion (AIC), increased the adjusted R^2, increased the loglikelihood, resulted in chi-square (X^2) greater than the associated critical X^2 value, and $p < 0.05$. To evaluate the robustness of the linear regression models, each model was used to calculate the relaxation times from a second trial of each participant. The mean standard error (SE) and RMSE of this second trial were calculated to evaluate the error of the final linear regression model. Final model results were reported as (estimate; p value). For each regression model, one representative participant with high MFPC scores and one participant with low MFPC scores were selected to aid interpretation of the results.

3 RESULTS

3.1 Participant Characteristics

Seventy-two participants (41 female; age: 51.4 ± 14.9 years old; body mass index (BMI): 24.3 ± 3.3 kg/m^2) were recruited for this study and both limbs analyzed (n = 144) (Figure 1). Of the hips, 32, 58, 31, and 23 hips were graded as KL 0, 1, 2, and 3, respectively. On average across the graded SHOMRI regions, 73%, 21%, and 6% of hips had intact cartilage, partial cartilage tears, or full cartilage tears, respectively; 29 of 32 (90%) hips with KL 0 had intact cartilage, while 35 of 112 (31%) hips with KL > 0 had partial or full cartilage tears (Table 2).

3.2 Multivariate Functional Principal Component Analysis

The first five sagittal and transverse plane MFPCs and the first four coronal plane MFPCs were selected as independent variables for the linear regression models (Figure 2) and accounted for at least 88.8% of variation in each plane (Supplemental Table 1).

3.3 Linear Regression Model Selection

The addition of the independent variables transverse MFPCs 3 and 5 to BMI provided information pertaining to femoral cartilage $T_{1\rho}$ relaxation times ($X^2 > 5.991$, $p = 0.006$) and were included in the final regression model (Supplemental Table 2). The addition of the independent variable transverse MFPC 2 to BMI provided information pertaining to femoral cartilage T_2 relaxation times ($X^2 > 3.841$, $p = 0.005$) and was included in the final regression model. The addition of the independent variable sagittal MFPC 1 to BMI provided information pertaining to acetabular cartilage $T_{1\rho}$ relaxation times ($X^2 > 3.841$, $p = 0.012$) and were included in the final regression model. The predicted relaxation times from a second trial of data had similar RMSEs to those of the initial model and mean SE < 1.451 ms (Supplemental Table 3).

3.4 MFPC Modes and BMI Related to Mean $T_{1\rho}$ Relaxation Times in the Femoral Cartilage

Transverse plane MFPC modes 3 (−0.020; $p = 0.015$) and 5 (0.034; $p = 0.046$) and BMI (0.400; $p < 0.001$) were significantly related with mean $T_{1\rho}$ relaxation times in the femoral cartilage. The model estimates indicated mean $T_{1\rho}$ relaxation times in the femoral cartilage decreased 0.020 ms and increased 0.034 and 0.400 ms per unit increase in transverse MFPC 3 and 5 and BMI, respectively (Table 3A). Transverse plane MFPC mode 3 was primarily characterized by a vertical shift in hip internal/external rotation (IR/ER), with small vertical shifts in ankle IR/ER (Figure 3A). Transverse plane MFPC mode 5 was characterized by differences in hip, knee, and ankle slope direction during midstance (Figure 3B). Greater hip and ankle external rotation and unchanged ankle IR/ER slopes during midstance were related to increased $T_{1\rho}$ relaxation times in the femoral cartilage. Participants 27 and 83 had representative low and high transverse MFPC 3 scores of −67.205 and 62.704, respectively, with $T_{1\rho}$ relaxation times in the femoral cartilage of 42.423 and 29.492 ms, respectively. The transverse MFPC 3 score of Participant 27 was 129.909 lower than Participant 83, which corresponded to a positive shift in hip and ankle rotation angles and a 12.931 ms increase in $T_{1\rho}$ relaxation times in the femoral cartilage (Figure 3A).

3.5 MFPC Modes and BMI Related to Mean T_2 Relaxation Times in the Femoral Cartilage

Transverse plane MFPC mode 2 (0.026; $p = 0.005$) and BMI (0.495; $p < 0.001$) were significantly related to mean T_2 relaxation times in the femoral cartilage. The model estimates indicated mean T_2 relaxation times in the femoral cartilage increased 0.0206 and 0.495 ms per unit increase in transverse MFPC 2 and BMI, respectively (Table 3B). Transverse MFPC 2 was primarily characterized by a vertical shift in knee IR/ER angles (Figure 4). Greater knee internal rotation was related to increased T_2 relaxation times in the femoral cartilage. Participants 9 and 7 had representative high and low transverse MFPC 2 scores of 155.003 and −51.166, respectively, with T_2 relaxation times in the femoral cartilage of 40.479 and 26.764 ms, respectively. The transverse MFPC 2 score of Participant 9 was 206.169 higher than Participant 7, which corresponded to a positive shift in knee rotation of approximately 20° and 13.715 ms increase in T_2 relaxation times in the femoral cartilage (Figure 4).

3.6 MFPC Modes and BMI Related to Mean $T_{1\rho}$ Relaxation Times in the Acetabular Cartilage

Sagittal plane MFPC mode 1 (0.008; $p = 0.013$) and BMI (0.506; $p < 0.001$) were significantly related to mean $T_{1\rho}$ relaxation times in the acetabular cartilage. The model estimates indicated mean $T_{1\rho}$ relaxation times in the acetabular cartilage increased 0.005 ms and 0.506 ms per unit increase in sagittal MFPC 1 and BMI, respectively (Table 3C). Sagittal MFPC 1 was primarily characterized by a vertical shift in hip and knee flexion during midstance (Figure 5). Lower hip, knee, and ankle flexion angles were related to increased $T_{1\rho}$ relaxation times in the acetabular cartilage. Participants 74 and 90 had representative high and low sagittal MFPC 1 scores of 143.686 and −129.031, respectively, with $T_{1\rho}$ relaxation times in the acetabular cartilage of 46.731 and 26.038 ms, respectively. The sagittal MFPC 1 score of Participant 74 was 272.717 higher than Participant 90, which corresponded to a negative shift in hip and knee flexion/extension of approximately 20° and 15°, respectively, and a 20.694 ms increase in $T_{1\rho}$ relaxation times in the acetabular cartilage (Figure 5).

3.7 BMI Related to Mean T_2 Relaxation Times in the Acetabular Cartilage

BMI was significantly related to mean T_2 relaxation times in the acetabular cartilage (0.549; $p < 0.001$). The model estimates indicated mean T_2 relaxation times in the acetabular cartilage increase 0.549 ms per unit increase in BMI (Table 3D).

4 DISCUSSION

This study employed a data-driven framework to identify relationships between multi-joint biomechanics and quantitative assessments of cartilage biochemical composition and health. These relationships could provide direction for hip OA interventions that are independent of BMI. This work emphasizes the usefulness of MFPCA to study gait in healthy and early-to-moderate hip OA participants and also demonstrates how combined hip, knee, and ankle angles can be analyzed to characterize gait variation across participants. Although MFPCA was used to analyze joint angles by plane of motion, this technique could be used to investigate waveform features across multiple planes and joints. Furthermore, this technique reduces the need to eliminate potentially meaningful biomechanics data and simplifies the interpretation of combined multi-joint waveform features.

The MFPC modes significantly related to femoral cartilage relaxation times were in the transverse plane, where greater internal rotation during gait was related to increased $T_{1\rho}$ and T_2 relaxation times. Participants with increased internal rotation during gait may be more prone to femoral cartilage degradation due to altered hip loading. The relationship between greater hip internal rotation and increased $T_{1\rho}$ relaxation times in the femoral cartilage supported previous work that reported hip OA participants had twice as much internal rotation at push-off during walking compared to controls.[14] Additionally, Eitzen et al. reported participants with hip OA had decreased hip IR/ER range of motion,[13] which was supported by the relationship between femoral $T_{1\rho}$ and the decreased hip range of motion exhibited by transverse MFPC 5 in the current study. However, Eitzen et al. defined hip OA as those with a Harris Hip Score between 60–95.[13] It is possible that these participants

were closer to moderate hip OA as a majority of the Harris Hip Score is comprised of pain severity and function[30], which are often affected later in this disease. The discord between these two previous studies highlights potential short-comings of averaging or condensing gait data. Multiple reports of hip OA participants with significant differences in transverse plane kinematics may signify that transverse plane kinematics are important to the development of hip OA, but should be assessed during gait analysis with adequate means that consider biomechanical waveform features.

Greater hip, knee, and ankle extension during gait may exert additional stresses on the acetabulum and may explain why sagittal MFPC 1 was related to higher $T_{1\rho}$ relaxation times in the acetabular cartilage. These increased extension angles may explain a previous study that reported hip OA progressors exhibited significant increases in $T_{1\rho}$ relaxation times localized in the superior acetabular cartilage.[16] The current results are in contrast to a PCA study by Meyer et al., which reported mild-to-moderate hip OA participants exhibited increased hip, knee, and ankle flexion.[31] However, these discrepancies between Meyer et al. and the current study may be the result of different hip OA definitions and/or data collection or analysis techniques. As the hip is part of the lower-limb kinematic chain, analysis of the biomechanics related to hip OA should encompass motion in all planes and at all joints. Additionally, these investigations should include waveform features, as it is these features that clinicians will seek to alter as an intervention and not a single point. Therefore, techniques such as MFPCA, in particular, are necessary to analyze waveform features, because the biomechanical waveform features of the hip, knee, and ankle can be combined and assessed simultaneously. This removes additional statistical analyses required in traditional methods that analyze joint or planar waveform features separately and then compare the PC scores after. Furthermore, the combined analysis of MFPCA would enable clinicians to easily see what changes need to be made at multiple joints during gait retraining.

There are limitations to this study that warrant discussion. Hip abductor integrity or pathology, such as tendinosis or tears, was not assessed for these participants, which could have an effect on coronal and transverse plane kinematics. Joint angles were normalized to stance phase, which has been shown to have an effect on FPCA results.[32] However, participants in the current study walked at the same speed, which would render temporal effects on the MFPCs negligible. One representative trial was analyzed, to prevent wash-out of any key variations in gait that can occur when gait trials are averaged. Several PCA studies employed mean trial data for each participant, but this practice was not explained in detail.[31; 33–35] In the absence of an external dataset for a complete validation of each regression model, we evaluated the ability of the regression models to calculate $T_{1\rho}$ and T_2 relaxation times from a second trial of gait data. Although the linear regression models were significantly improved with the addition of MFPCs, we acknowledge that this did not substantially improve the predictive strength of the models. However, our goal was to characterize gait variation and determine if gait waveform features were related to cartilage relaxation times. Specifically, we sought to identify modifiable gait waveform features in addition to known factors, such as BMI and age, for future hip OA interventional studies. This framework was developed using linear regression to evaluate relationships between

these waveform features and relaxation times, but we could have related these waveform features to other measures of hip health, such as KL scores, pain, or functional tests.

These results highlight the potential of MFPCA to identify waveform features in biomechanical data that are related to biochemical evidence of hip OA. Specifically, increased internal rotation across the hip, knee, and ankle was related to femoral cartilage degradation, while decreased flexion across these three joints was related to acetabular cartilage degradation. These results may indicate that the femoral cartilage biochemistry is more sensitive to changes in lower-limb joint rotation, while the acetabular cartilage is more sensitive to alterations in the sagittal plane. The increased use of waveform feature analysis, such as MFPCA, may improve gait and motion analysis techniques and gait retraining, by promoting the modification of a curve segment instead of a single point. Furthermore, the simultaneous characterization of motion across multiple joints in this study prevented the sacrifice of kinematic trends common with other statistical techniques. The outcomes of this work provide credit to the ability of MFPCA to reduce the dimensionality of continuous temporal data and could prove a useful feature extraction technique for machine learning. Future studies will be necessary to determine if these waveform features can be used to longitudinally predict quantitative measures of hip OA and cartilage health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Control CfD Prevention U.2009. Prevalence and most common causes of disability among adults--United States, 2005. MMWR Morb Mortal Wkly Rep58:421–426. [PubMed: 19407734]
2. Yelin E, Murphy L, Cisternas MG, et al.2007. Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. Arthritis Rheumatol56:1397–1407.
3. Jordan JM, Helmick CG, Renner JB, et al.2009. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. J Rheumatol36:809–815. [PubMed: 19286855]
4. Maillefert JF, Gueguen A, Monreal M, et al.2003. Sex differences in hip osteoarthritis: results of a longitudinal study in 508 patients. Ann Rheum Dis62:931–934. [PubMed: 12972469]
5. Gandhi R, Wasserstein D, Razak F, et al.2010. BMI independently predicts younger age at hip and knee replacement. Obesity (Silver Spring)18:2362–2366. [PubMed: 20379147]
6. Bliddal H, Leeds AR, Stigsgaard L, et al.2011. Weight loss as treatment for knee osteoarthritis symptoms in obese patients: 1-year results from a randomised controlled trial. Ann Rheum Dis70:1798–1803. [PubMed: 21821622]
7. Christensen R, Astrup A, Bliddal H. 2005. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. Osteoarthritis Cartilage13:20–27. [PubMed: 15639633]
8. Ganz R, Leunig M, Leunig-Ganz K, et al.2008. The etiology of osteoarthritis of the hip: an integrated mechanical concept. Clin Orthop Relat Res466:264–272. [PubMed: 18196405]

9. Frost HM. 1994. Perspectives: a biomechanical model of the pathogenesis of arthroses. Anat Rec240:19–31. [PubMed: 7810912]
10. Shakoor N, Hurwitz DE, Block JA, et al.2003. Asymmetric knee loading in advanced unilateral hip osteoarthritis. Arthritis Rheumatol48:1556–1561.
11. Hurwitz DE, Hulet CH, Andriacchi TP, et al.1997. Gait compensations in patients with osteoarthritis of the hip and their relationship to pain and passive hip motion. J Orthop Res15:629–635. [PubMed: 9379275]
12. Judd DL, Dennis DA, Thomas AC, et al.2014. Muscle strength and functional recovery during the first year after THA. Clin Orthop Relat Res472:654–664. [PubMed: 23817756]
13. Eitzen I, Fernandes L, Nordsletten L, et al.2012. Sagittal plane gait characteristics in hip osteoarthritis patients with mild to moderate symptoms compared to healthy controls: a cross-sectional study. BMC Musculoskelet Disord13:258. [PubMed: 23256709]
14. Watelain E, Dujardin F, Babier F, et al.2001. Pelvic and lower limb compensatory actions of subjects in an early stage of hip osteoarthritis. Arch Phys Med Rehabil82:1705–1711. [PubMed: 11733886]
15. Pedoia V, Russell C, Randolph A, et al.2016. Principal component analysis-T1rho voxel based relaxometry of the articular cartilage: a comparison of biochemical patterns in osteoarthritis and anterior cruciate ligament subjects. Quant Imaging Med Surg6:623–633. [PubMed: 28090441]
16. Gallo MC, Wyatt C, Pedoia V, et al.2016. T1rho and T2 relaxation times are associated with progression of hip osteoarthritis. Osteoarthritis Cartilage24:1399–1407. [PubMed: 26973330]
17. Wyatt C, Kumar D, Subburaj K, et al.2015. Cartilage T1rho and T2 Relaxation Times in Patients With Mild-to-Moderate Radiographic Hip Osteoarthritis. Arthritis Rheumatol67:1548–1556. [PubMed: 25779656]
18. Duvvuri U, Reddy R, Patel SD, et al.1997. T1rho-relaxation in articular cartilage: effects of enzymatic degradation. Magn Reson Med38:863–867. [PubMed: 9402184]
19. Sahlman J, Inkinen R, Hirvonen T, et al.2001. Premature vertebral endplate ossification and mild disc degeneration in mice after inactivation of one allele belonging to the Col2a1 gene for Type II collagen. Spine (Phila Pa 1976)26:2558–2565. [PubMed: 11725236]
20. Hunter DJ, Guermazi A, Lo GH, et al.2011. Evolution of semi-quantitative whole joint assessment of knee OA: MOAKS (MRI Osteoarthritis Knee Score). Osteoarthritis Cartilage19:990–1002. [PubMed: 21645627]
21. Kellgren JH, Lawrence JS. 1957. Radiological assessment of osteo-arthrosis. Ann Rheum Dis16:494–502. [PubMed: 13498604]
22. Happ C, Greven S. 2018. Multivariate Functional Principal Component Analysis for Data Observed on Different (Dimensional) Domains. J Am Stat Assoc113:649–659.
23. Lee S, Nardo L, Kumar D, et al.2015. Scoring hip osteoarthritis with MRI (SHOMRI): A whole joint osteoarthritis evaluation system. J Magn Reson Imaging41:1549–1557. [PubMed: 25139720]
24. Li X, Wyatt C, Rivoire J, et al.2014. Simultaneous acquisition of T1rho and T2 quantification in knee cartilage: repeatability and diurnal variation. J Magn Reson Imaging39:1287–1293. [PubMed: 23897756]
25. Pedoia V, Li X, Su F, et al.2016. Fully automatic analysis of the knee articular cartilage T1rho relaxation time using voxel-based relaxometry. J Magn Reson Imaging43:970–980. [PubMed: 26443990]
26. Samaan MA, Zhang AL, Popovic T, et al.2019. Hip joint muscle forces during gait in patients with femoroacetabular impingement syndrome are associated with patient reported outcomes and cartilage composition. J Biomech84:138–146. [PubMed: 30600097]
27. Samaan MA, Schwaiger BJ, Gallo MC, et al.2017. Abnormal Joint Moment Distributions and Functional Performance During Sit-to-Stand in Femoroacetabular Impingement Patients. PM R9:563–570. [PubMed: 27729286]
28. Ryan W, Harrison A, Hayes K. 2006. Functional data analysis of knee joint kinematics in the vertical jump. Sports Biomech5:121–138. [PubMed: 16521626]
29. Kokoszka P, Reimherr M. 2017. Introduction to functional data analysis. Boca Raton: CRC Press, Taylor & Francis Group; xvi, 290 pages p.

30. Harris WH. 1969. Traumatic arthritis of the hip after dislocation and acetabular fractures: treatment by mold arthroplasty. An end-result study using a new method of result evaluation. J Bone Joint Surg Am51:737–755. [PubMed: 5783851]

31. Meyer CA, Corten K, Fieuws S, et al.2015. Biomechanical gait features associated with hip osteoarthritis: Towards a better definition of clinical hallmarks. J Orthop Res33:1498–1507. [PubMed: 25982594]

32. Epifanio I, Avila C, Page A, et al.2008. Analysis of multiple waveforms by means of functional principal component analysis: normal versus pathological patterns in sit-to-stand movement. Med Biol Eng Comput46:551–561. [PubMed: 18392871]

33. Wrigley AT, Albert WJ, Deluzio KJ, et al.2005. Differentiating lifting technique between those who develop low back pain and those who do not. Clin Biomech (Bristol, Avon)20:254–263.

34. Brandon SC, Graham RB, Almosnino S, et al.2013. Interpreting principal components in biomechanics: representative extremes and single component reconstruction. J Electromyogr Kines23:1304–1310.

35. Kobsar D, Osis ST, Hettinga BA, et al.2015. Gait Biomechanics and Patient-Reported Function as Predictors of Response to a Hip Strengthening Exercise Intervention in Patients with Knee Osteoarthritis. PLoS One10:e0139923.

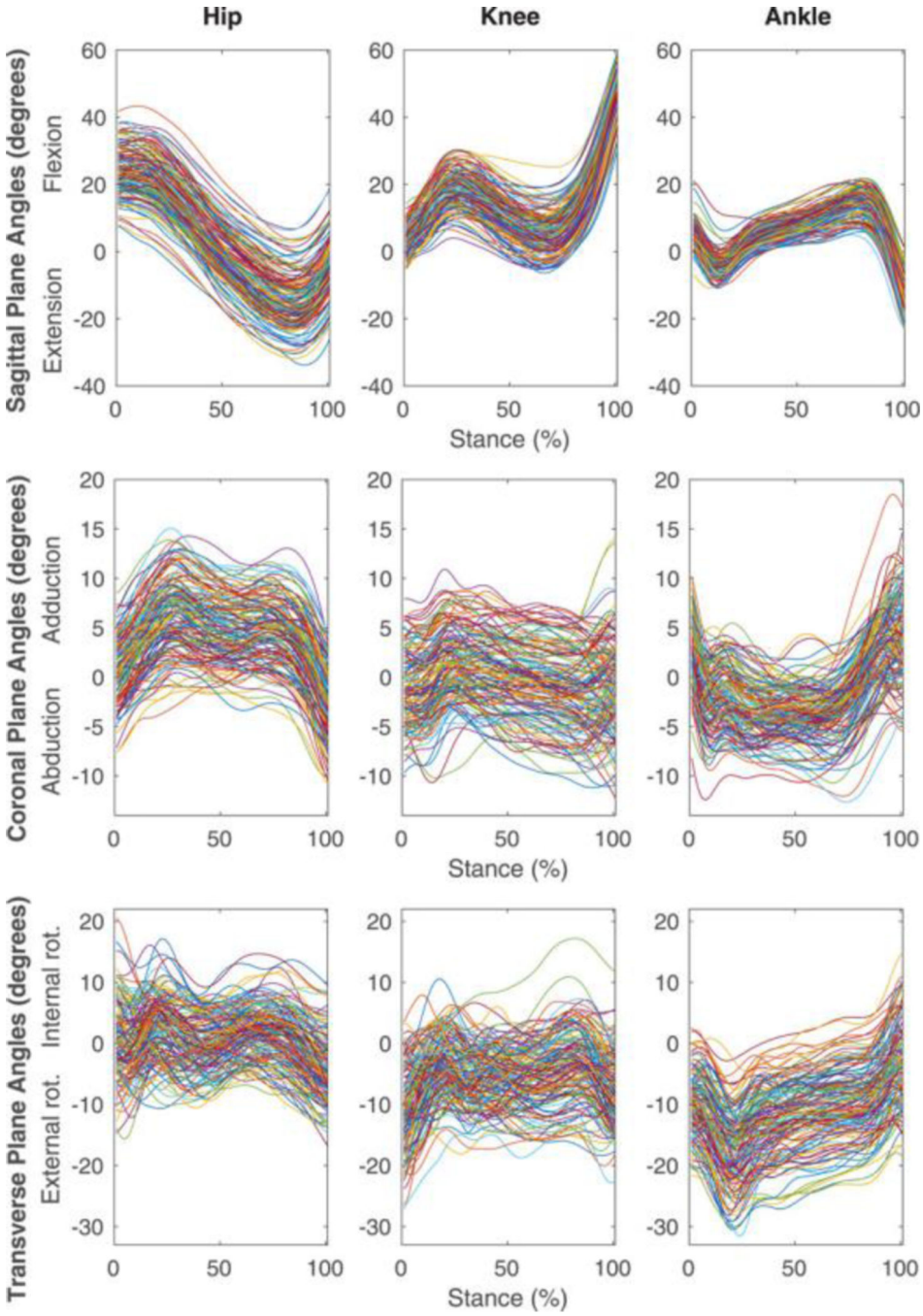

Figure 1:

Sagittal (top), coronal (middle), and transverse (bottom) plane hip (left), knee (center), and ankle (right) angles from 72 participants (144 lower-limbs) with mild-to-moderate hip osteoarthritis (Kellgren-Lawrence grade 0–3) during the stance phase of gait. Each line represents a joint angle from a different limb.

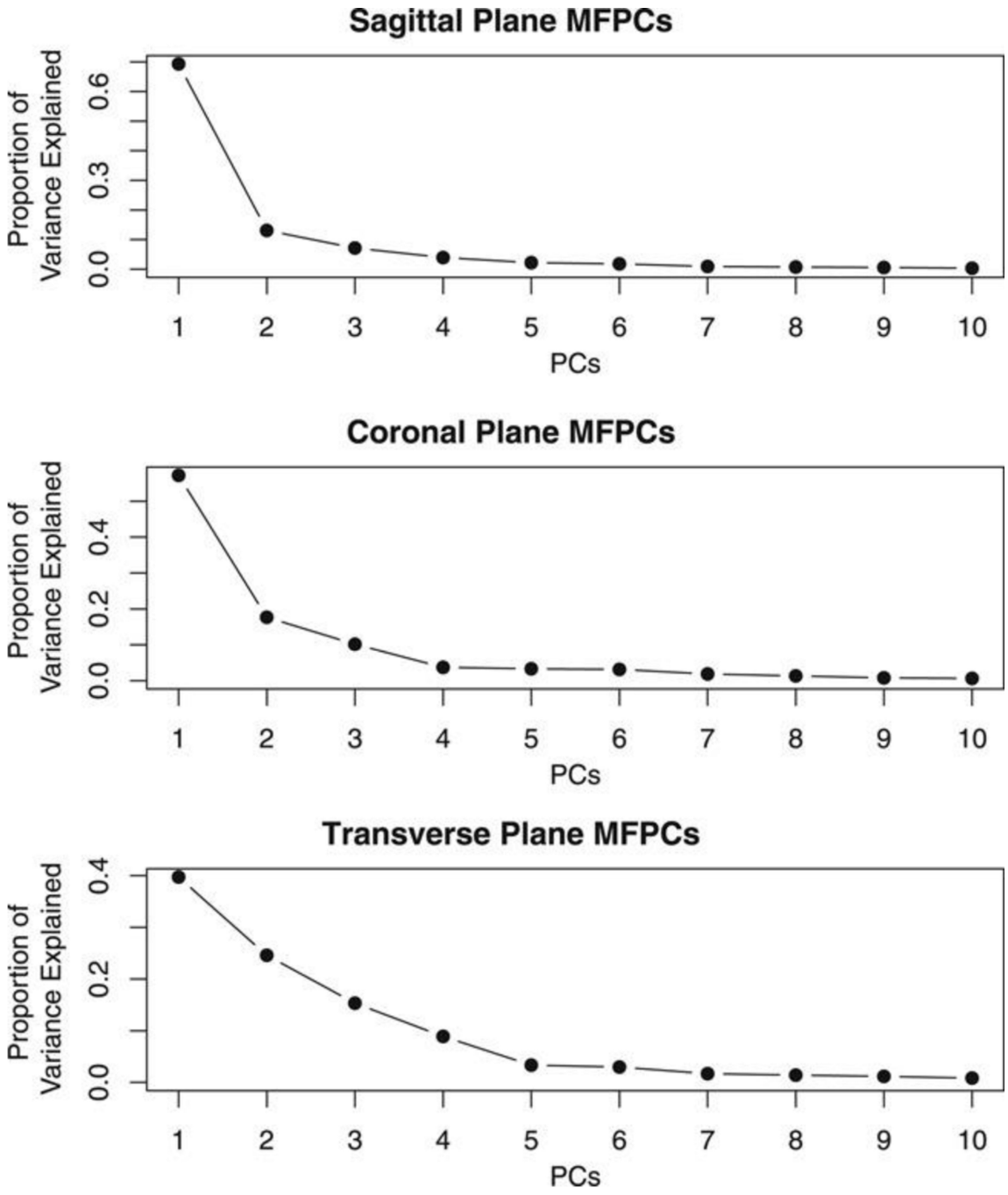

Figure 2:

Screeplots of the proportion of variance explained by each multivariate functional principal component (MFPC) in the sagittal (top), coronal (center), and transverse (bottom) planes. The point of diminishing returns was used to determine how many MFPCs to include in the linear regression models.

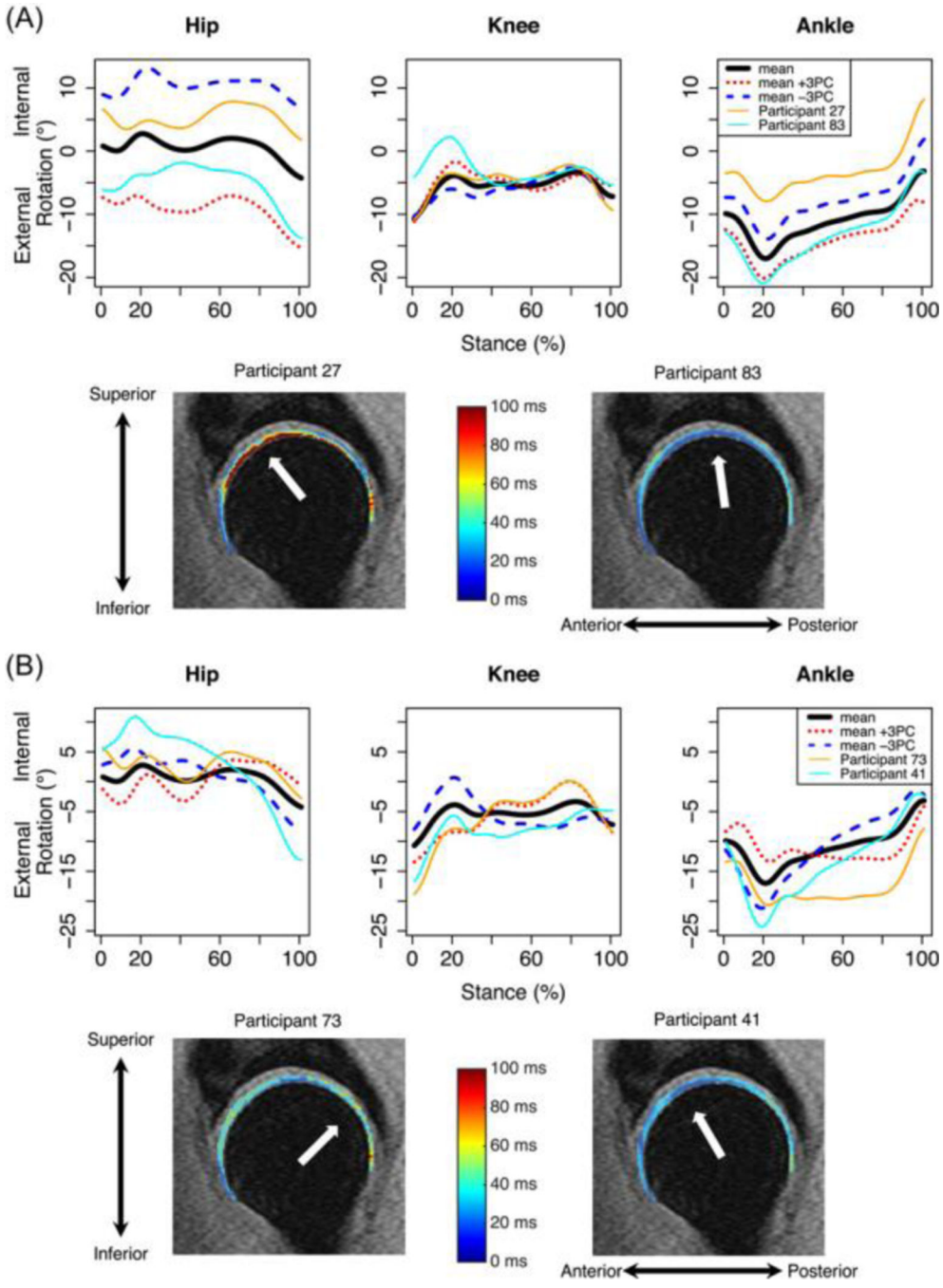

Figure 3:

A: Mean hip (left), knee (center), and ankle (right) angles plus or minus three standard deviations of the variance of transverse plane multivariate functional principal component (MFPCs) 3, which was related to mean $T_{1\rho}$ relaxation times in the femoral cartilage. Transverse MFPC 3 was primarily characterized by a vertical shift in hip internal/external rotation (IR/ER), with small vertical shifts in ankle IR/ER. Representative examples of participants with high (Participant 27, orange lines) and low (Participant 83, cyan lines) transverse MFPC 3 scores (top) and corresponding $T_{1\rho}$ maps (bottom) for each participant

with arrows indicating regions of high (left) and low (right) relaxation times. Colormap (bottom) is of $T_{1\rho}$ relaxation times in the cartilage. **B:** Mean hip (left), knee (center), and ankle (right) angles plus or minus three standard deviations of the variance of transverse plane MFPC 5, which was related to mean $T_{1\rho}$ relaxation times in the femoral cartilage. Transverse MFPC 5 was characterized by differences in hip, knee, and ankle slope direction during midstance. Representative examples of participants with high (Participant 73, orange lines) and low (Participant 41, cyan lines) transverse MFPC 5 scores (top) and corresponding $T_{1\rho}$ maps (bottom) for each participant with arrows indicating regions of high (left) and low (right) relaxation times. Colormap (bottom) is of $T_{1\rho}$ relaxation times in the cartilage. Internal rotation is positive; external rotation is negative.

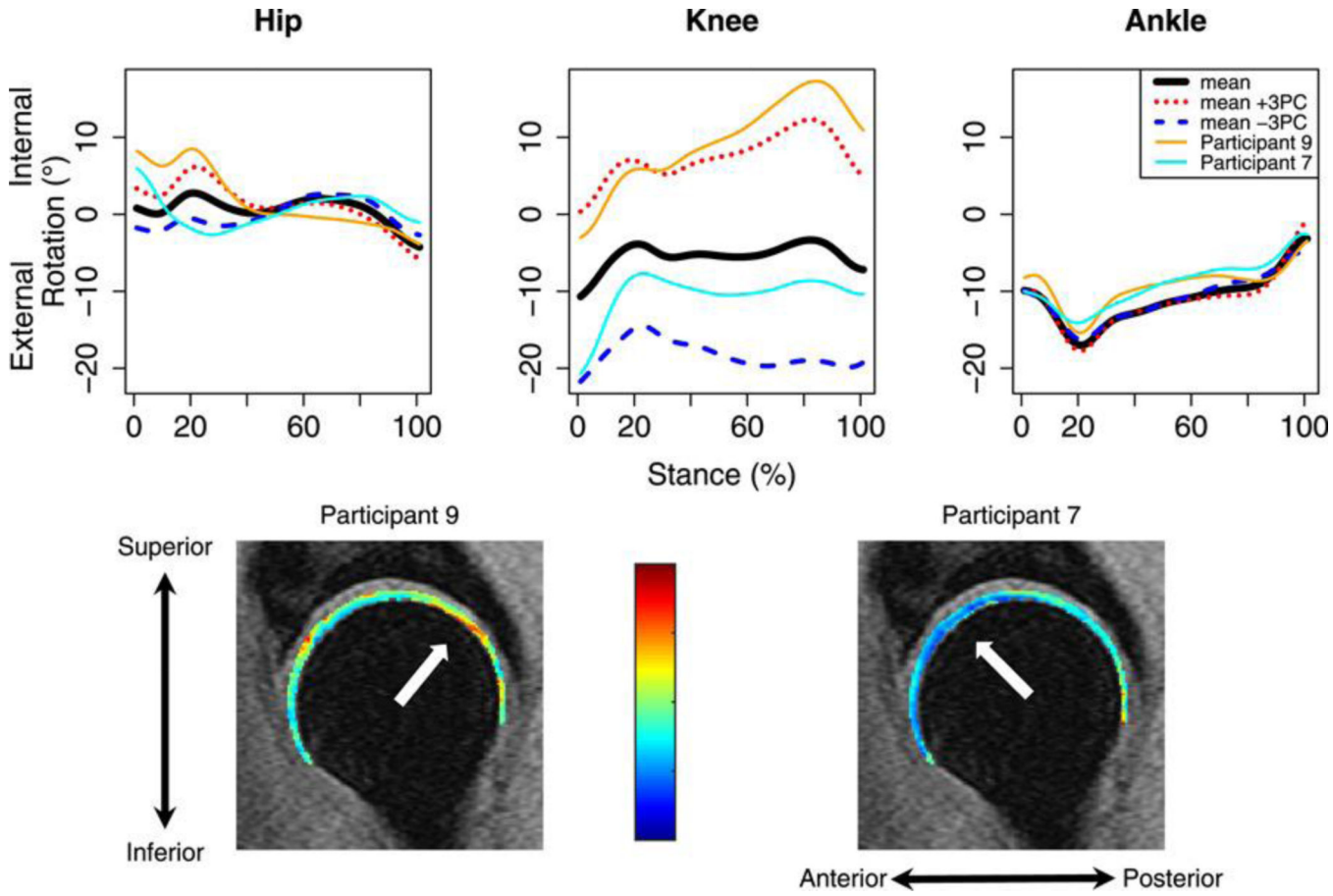

Figure 4:

Mean hip (left), knee (center), and ankle (right) angles plus or minus three standard deviations of the variance of transverse plane multivariate functional principal component (MFPC) 2, which was related to mean T_2 relaxation times in the femoral cartilage. Internal rotation is positive; external rotation is negative. Transverse MFPC 2 was primarily characterized by a vertical shift in knee internal/external rotation angles. Representative examples of participants with high (Participant 9, orange lines) and low (Participant 7, cyan lines) transverse MFPC 2 scores (top) and corresponding T_2 maps (bottom) for each participant with arrows indicating regions of high (left) and low (right) relaxation times in the femoral cartilage. Colormap (bottom) is of T_2 relaxation times in the cartilage.

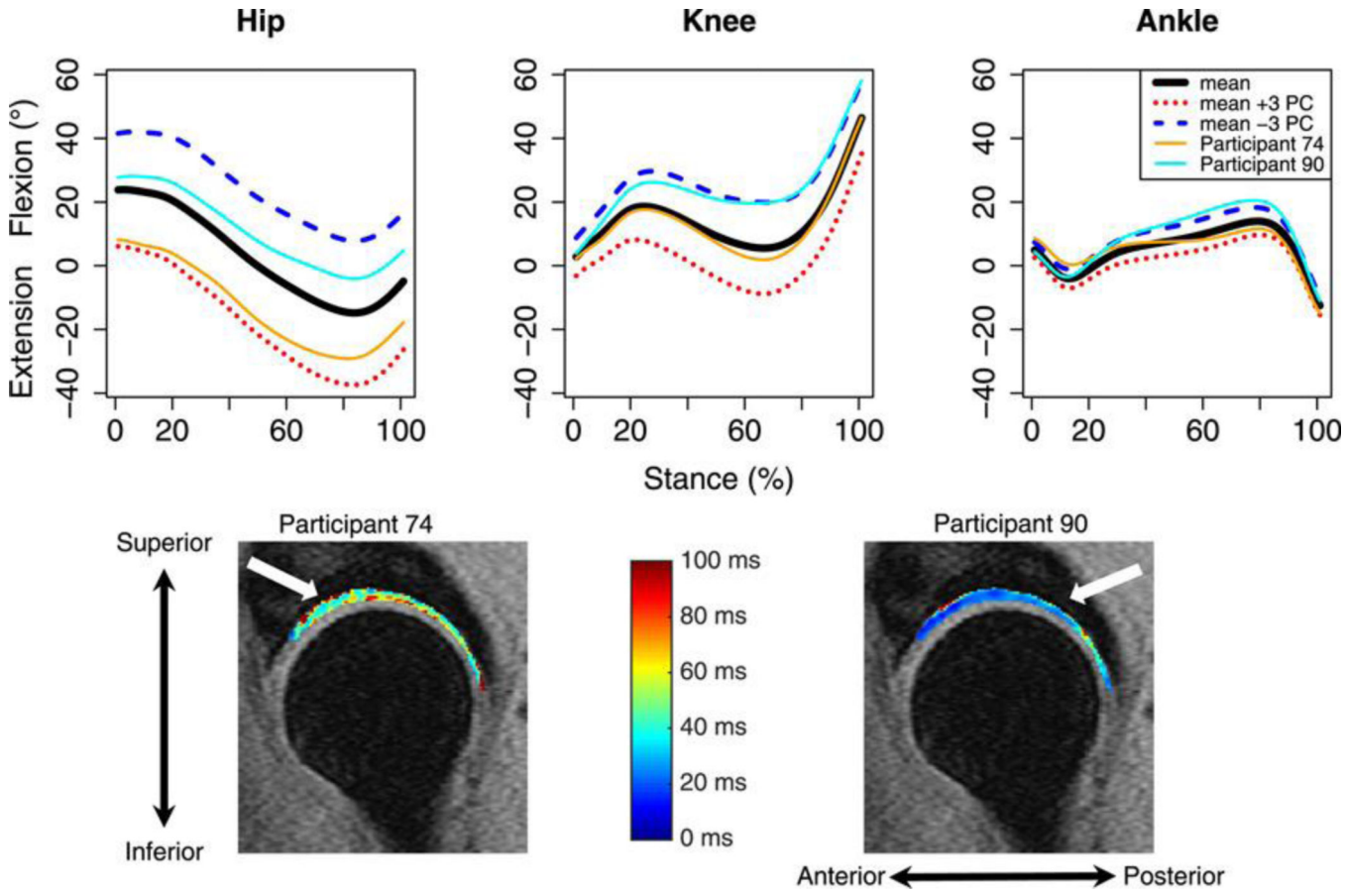

Figure 5:

Mean hip (left), knee (center), and ankle (right) angles plus or minus three standard deviations of the variance of sagittal plane multivariate functional principal component (MFPC) 1, which was related to mean $T_{1\rho}$ relaxation times in the acetabular cartilage. Flexion is positive; extension is negative. Sagittal MFPC 1 was primarily characterized by a vertical shift in hip flexion and knee flexion during midstance. Representative examples of participants with high (Participant 74, orange lines) and low (Participant 90, cyan lines) sagittal MFPC 1 scores (top) and corresponding $T_{1\rho}$ maps (bottom) for each participant with arrows indicating regions of high (left) and low (right) relaxation times. Colormap (bottom) is of $T_{1\rho}$ relaxation times in the cartilage.

Table 1:

Imaging sequence, acquisition parameters, resolution, and measurement application of the magnetic resonance (MR) protocol.

Imaging Sequence	Acquisition Parameters	Resolution	Measurements
3 plane GRE **(41 s)**			Localizer – for coverage
Coronal T_2 FS **(5 min)**	TR/TE = 3000/60.0 ms; receiver bandwidth = 41.67 Hz; echo train length = 12; NEX = 6; FOV = 20 cm; matrix size = 288×192; slice thickness = 4.0 mm	0.7 × 1.0 × 4.0 mm^3	SHOMRI scoring
3D FSE-CUBE FS **(10 min)**	TR/TE = 1200/20 ms; echo receiver bandwidth = 50 Hz; train length = 30; FOV = 15.3 cm; matrix size = 192×192; slice thickness = 0.8 mm	0.8 × 0.8 × 0.8 mm^3	SHOMRI scoring
Combined $T_{1\rho}$ and T_2 mapping **(10 min)** MAPSS (sagittal)	TE = 0, 10.4, 20.8, 41.6 ms; TSL = 0/15/30/45 ms; receiver bandwidth =62.50 kHz; NEX=1; FOV=14 cm; views per segment = 64; TR = 1.2 s; Spin Lock Frequency = 300 Hz; matrix size = 256×128; slice thickness = 4.0 mm	0.6 × 1.0 × 4.0 mm^3	Cartilage segmentation and femoral and acetabular cartilage $T_{1\rho}$ and T_2 quantification

Table 2:

Magnetic resonance imaging (MRI) clinical characteristics (Scoring hip osteoarthritis with MRI, SHOMRI) cartilage lesion scores for acetabulum and femoral head regions of participant hips with Kellgren Lawrence (KL) scores of 0 and KL scores > 0[a]

SHOMRI cartilage lesion score	Acetabulum		Femoral Head			
	superior lateral	superior medial	lateral	superior lateral	superior medial	inferior medial
KL 0 (n=32 hips)						
Intact	25 (17%)	28 (19%)	28 (19%)	30 (21%)	31 (22%)	30 (21%)
Partial tear	6 (4%)	2 (1%)	4 (3%)	2 (1%)	1 (1%)	2 (1%)
Full tear	1 (1%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
KL > 0 (n=112 hips)						
Intact	46 (32%)	79 (55%)	75 (52%)	71 (49%)	89 (62%)	103 (72%)
Partial tear	60 (42%)	24 (17%)	26 (18%)	33 (23%)	13 (9%)	5 (3%)
Full tear	6 (4%)	9 (6%)	11 (8%)	8 (6%)	10 (7%)	4 (3%)

[a]Data expressed as count (percentage of total sample %).

Table 3:

Stepwise linear regression results for multivariate functional principal component modes in the sagittal (sag), coronal (cor), and transverse (tran) planes, age, gender, and BMI as independent variables and mean $T_{1\rho}$ relaxation times in the femoral cartilage **(A)**, T_2 relaxation times in the femoral cartilage **(B)**, $T_{1\rho}$ relaxation times in the acetabular cartilage **(C)**, and T_2 relaxation times in the acetabular cartilage **(D)** as dependent variables.

Table 3A: Femoral cartilage $T_{1\rho}$ regression model

	Estimate	SE	tStat	P value
(Intercept)	26.982	2.038	13.243	< 0.001
tran_PC3	-0.020	0.008	-2.458	0.015
tran_PC5	0.034	0.017	2.016	0.046
BMI	0.400	0.083	4.814	< 0.001

Model Summary:

Degrees of freedom: 140, **RMSE:** 3.258,
Adjusted R^2: 0.169, **F-statistic:** 10.670, **P-value:** < 0.001

Table 3B: Femoral cartilage T_2 regression model

	Estimate	SE	tStat	P value
(Intercept)	20.880	2.900	7.200	< 0.001
tran_PC2	0.026	0.009	2.831	0.005
BMI	0.495	0.118	4.182	< 0.001

Model Summary:

Degrees of freedom: 141, **RMSE:** 4.657,
Adjusted R^2: 0.124, **F-statistic:** 11.090, **P-value:** < 0.001

Table 3C: Acetabular cartilage $T_{1\rho}$ regression model

	Estimate	SE	tStat	P value
(Intercept)	24.273	1.984	12.232	< 0.001
sag_PC1	0.008	0.003	2.516	0.013
BMI	0.506	0.081	6.244	< 0.001

Model Summary:

Degrees of freedom: 141, **RMSE:** 3.222,
Adjusted R^2: 0.243, **F-statistic:** 23.910, **P-value:** < 0.001

Table 3D: Acetabular cartilage T_2 regression model

	Estimate	SE	tStat	P value
(Intercept)	18.778	2.749	6.830	< 0.001
BMI	0.549	0.112	4.895	< 0.001

Model Summary:

Degrees of freedom: 142, **RMSE:** 4.475,
Adjusted R^2: 0.138, **F-statistic:** 23.960, **P-value:** < 0.001

SE = standard error; tStat = t statistic; RMSE = root mean squared error.