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Detrimental effects of long sedentary bouts on the biomechanical response of cartilage to sliding

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ABSTRACT

Purpose/Aim: Epidemiological evidence suggests, contrary to popular mythos, that increased exercise/joint activity does not place articular cartilage at increased risk of disease, but instead promotes joint health. One explanation for this might be activity-induced cartilage rehydration; where joint articulation drives restoration of tissue hydration, thickness, and dependent tribomechanical outcomes (e.g., load support, stiffness, and lubricity) lost to joint loading. However, there have been no studies investigating how patterning of intermittent articulation influences the hydration and biomechanical functions of cartilage.

Materials and Methods: Here we leveraged the convergent stationary contact area (cSCA) testing configuration and its unique ability to drive tribological rehydration, to elucidate how intermittency of activity affects the biomechanical functions of bovine stifle cartilage under well-controlled sliding conditions that have been designed to model a typical "day" of human joint activity.

Results: For a fixed volume of "daily" activity (30 min) and sedentary time (60 min), breaking up intermittent activity into longer and less-frequent bouts (corresponding to longer continuous sedentary periods) resulted in the exposure of articular cartilage to markedly greater strains, losses of interstitial pressure, and friction coefficients.

Conclusions: These results demonstrated that the regularity of *ex vivo* activity regimens, specifically the duration of sedentary bouts, had a dominant effect on the biomechanical functions of articular cartilage. In more practical terms, the results suggest that brief but regular movement patterns (*e.g.*, every hour) may be biomechanically preferred to long and infrequent movement patterns (*e.g.*, a long walk after a sedentary day) when controlling for daily activity volume (*e.g.*, 30 min).

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Introduction

Recent evidence comparing long-term historical trends in knee osteoarthritis (OA) in the United States highlight a doubling in OA prevalence since the mid-twentieth century, even after controlling for age, body mass index, and other variables.[1] These data point to OA risk factors that are unique to or amplified in modern society, leading to the postulate of OA being a 'mismatch disease';[2] a disease thought to be more prevalent or severe because the human body is inadequately or imperfectly adapted to the environment or sociodemographic changes associated with modernity.[3]

A major factor implicated in many mismatch diseases, and one of specific interest to the study of OA, is our increasingly sedentary lifestyle. On average, American adults spend up to 10 out of 16 waking hours sedentary,[4,5] and both sedentary volume and the lengths of uninterrupted bouts of inactivity appear to be increasing. Additionally, only ~20% of adults engage in the recommended 30 min of daily physical exercise.[6] While evidence supporting the overall health benefits of physical activity are clear,[7] there remains a somewhat popular mythos that the "wear and tear" associated with exercise and a healthy active lifestyle might act to compromise joint health.[8] Whereas links between joint injury,[9,10] obesity,[11,12] and joint disease are well established, causal relationships between exercise/inactivity and joint health have been more difficult to tease out. A recent review of case studies have found that when controlling for injury, populations participating in moderate amounts of non-competitive recreational exercise experienced no significant increase in OA risk, while less active cohorts tend to experience increased risks.[8] For example, among runners, one study found that those logging more than 12.9 km/week experienced significantly reduced risk of OA compared to their most sedentary peers.[13] These observations suggest a far

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The supplementary data for this article can be accessed here.

more complex OA disease etiology than that of just simple use-driven wear and tear, motivating a need for additional research into the links between joint activity, function, and disease.

If physical activity is a prerequisite for joint longevity, what mechanisms underlie such benefit? Modulation of joint development, obesity, and metabolic inflammation represent pathways by which activity could reduce OA risk.[2] However, because of cartilage's biphasic nature, purely biomechanical benefits of exercise on tissue health are possible as well. Cartilage is highly-hydrated (70–80% water wt/vol),[14] thus mechanical loading drives pressurization of its interstitial fluid. This pressurization allows for the fluid-born support of compressive stresses, stiffening of the cartilage, and shielding of the ECM from stresses; together, these outcomes, through the mechanisms of interstitial lubrication,[15] allow the tissue to realize substantial reductions in friction when articulation is initiated.[16] Nonetheless, under sustained loads, cartilage thins/strains due to pressure-induced fluid exudation,[17] driving a loss of interstitial fluid pressure and the defeat of numerous biomechanical functions, including lubricity.[16] It is this exudative process, and the associated defeat of lubrication, that underlie the intuition of activity being a contributor to OA via 'wear and tear'.[18] However, upon articulation, it has been observed that cartilage and joint space thinning can be halted and reversed, indicating that joint activity can help to retain and restore cartilage's interstitial hydration and biomechanical function.[19–21] Because cartilage's biomechanical functions are dependent upon a competition between load-induced "dehydration" and articulation-induced "rehydration", one could posit, somewhat counterintuitively, that exercise could drive improved biomechanical function and longevity of cartilage through activity-induced "rehydration".

Indeed, well-established links between joint movement, and the hydration, mechanical function, and cellular function of cartilage suggest that regular exercise is necessary to maintain the mechanical function, and homeostasis of articular cartilage. However, practical matters, such as the quantity or frequency of activity necessary to promote optimal tissue function and joint longevity remain to be settled. While at least 30 min of moderate intensity activity (e.g., running, brisk walking, bicycling, etc.) per day is recommended for its overall health benefits,[22,23] no guidance is available regarding how well this satisfies demands specific to joints, nor how the prescribed 30-plus minutes of daily activity should be administered to maximize functional benefit.[24] For example, recent research indicates that prolonged sedentary bouts are associated with all-cause mortality[5,25] and can reduce or negate the overall health benefits of exercise.[26] Biphasic tissue theory also suggests that prolonged sedentary bouts could have negative implications for cartilage function. However, there has been a lack of studies, epidemiological or otherwise, investigating how the patterning of daily activities might affect the biomechanical functions of cartilage.

A barrier to studying cartilage biomechanics in the context of intermittent activity is the difficulty in achieving both experimental control and physiological consistency. In prior studies,[27–31] we identified that the convergent stationary contact area (cSCA) configuration, first described and used by Walker and Dowson,[32] provides a unique benchtop explant model for studying these relationships under a combination of experimental control, measurement resolution, and physiological-consistency not available with other cartilage explant contact configurations. Similar to articulation in the joint, we have shown that high-speed sliding (>30 mm/s) in the cSCA promotes a competitive recovery of cartilage's interstitial fluid and actively counteracts exudation driven by compression.[27,30] This competitive rehydration process contrasts with the unmitigated exudation seen in the SCA and the explicit prevention of fluid flow and interstitial pressure losses of the MCA. We termed this sliding-induced recovery phenomenon 'tribological rehydration'[27] to reflect the fact that recovery is a consequence of sliding rather than contact unloading or migration. More importantly, we demonstrated that continuous high-speed sliding in the cSCA configuration could i) restore, promote, and maintain physiologically consistent tissue strains (0–20%); ii) sustain unprecedently low, yet physiologically-consistent steady-state friction magnitudes ($\mu < 0.05$) over long-term testing (hours) *ex vivo*,[27,28] and iii) do so in a manner that is dependent upon sliding speed and contact geometry, and is thus consistent with a hydrodynamic phenomenon.[27,30]

In the current study, we leveraged the unique attributes of the cSCA explant testing configuration to investigate—through the application of fixed overall volumes of sliding "activity" (30 min), static "sedentary" loading (60 min), and "overnight" unloading (60 min)—how intermittent sedentary bout lengths influence cartilage's hydration-dependent biomechanics in responses to a modeled "day" of typical joint activity. We demonstrated that shortening the continuous length of time cartilage spent "sedentary", by implementing more frequent bouts of high-speed [100 mm/s] sliding, could significantly reduce and more quickly recover interstitial hydration, pressure, cartilage thickness, and lubrication lost to the influence of physiologically-relevant compressive stresses (~0.2 MPa). These results suggest that, in the cSCA, the biomechanical functions of cartilage (e.g.,

the minimization of tissue strain and maintenance of high lubricity) are better sustained by shorter and more-frequent activity patterns than by longer and less-frequent activities, and that similar relationships might be relevant to cartilage function and longevity *in vivo*.

Materials and methods

Specimens

Five, 19 mm diameter osteochondral cores were extracted from the centerline of the medial and lateral femoral condyles of three previously frozen and defrosted (thawed overnight at 4°C) mature bovine stifle joints (Bowman's Butcher Shop, Churchville, MD). Samples were refrigerated in 1X phosphate buffered saline (PBS) containing protease inhibitors (P2714, Sigma Aldrich) at 4°C and tested within 4 days of harvest.

Explant testing instrument

Schematics of the custom-built *in situ* pin-on-disk material tester and the nature of the sliding environment are shown in Figure 1(A–C) (details regarding this materials tester have been reported previously).[30] Cartilage explants were mated against a glass disk lubricated with PBS supplemented with protease inhibitors in the cSCA configuration, which is distinguished from the SCA only by the presence of a convergent wedge at the leading edge of the contact. This convergent wedge is required for driving sliding-induced tribological rehydration (Figure 1C) and forms when the explant sample is convex and larger in diameter than that of the glass-on-cartilage contact.[27] Each explant was oriented such that *ex vivo* sliding was performed in line with the principle direction of sliding between the condyle and tibial plateau *in vivo*. Sliding speed was controlled using a stepper motor and load was applied and controlled using a nanopositioning stage with normal force feedback from a six-channel load cell. Normal force (F_n), friction force (F_f), and deformation (δ) were measured directly and continuously throughout the experiment.

Simulating an "equivalent day"

A loading protocol was designed to model aspects of loading and activity patterning experienced during the course of an equivalent human "day" (Figure 1(D–E)), requiring a scaling of time based upon exudation dynamics, which is proportional to contact area.[31] Compared to *in vivo* measurements under similar loads,[33,34] cSCA contact areas are ~10% of those estimated for the human knee. Thus, we defined an equivalent day as 150 min or ~10% of a 24-h day. Diurnal loading was implemented by breaking each 150-min "equivalent day" into one 90 min loaded period of constant 5N compressive load (resulting in an ~0.2 MPa contact stress) to simulate a 15 h "awake" phase, and one 60 min recovery period of constant 0.1 N load (resulting in a ~10 kPa contact stress) to allow passive recovery during the "sleep" phase. The compressive stresses applied during the "awake" period was consistent with average contact stresses experienced in knee and hip joints during awake activity (0.1–1.0 MPa).[35–37] The nominal load applied during the "sleep" period was intended to model the presence of non-zero ligament and muscle tension and positional stresses across the "unloaded" joint during overnight rest, to prevent surface separation ("liftoff") during load-controlled testing, and to provide an osmotic "resting" equilibrium for comparisons to *in vivo* measurements of joint space.

Each 90-min awake phase (5 N) was further divided into 60-min of static loading and 30 min of sliding at a fixed speed of 100 mm/s; this sliding speed approximates *in vivo* articulation speeds[38] (See Supplemental Material S.1 for estimates of *in vivo* sliding speeds) and 30 min of activity approximates the CDC's and WHO's minimum daily recommended amount.[6,23] The 30 min of sliding was administered in 1, 3, 5, 15, or 30 equally-sized and equally-spaced active bouts (30, 10, 6, 2, or 1 min each, respectively; Figure 1F, Supplemental Table 4) interposed with sedentary bouts twice the duration of each active bout (60 min of sedentary volume, in 60, 20, 12, 4, or 2-min lengths, respectively). These patterns will be referred to as "activity regimens" herein.

Preconditioning

Each sample was mounted in the materials tester and given 10 min to equilibrate in the PBS bath. The sample was then run-in (preconditioned) with an initial 150-min equivalent day. Briefly, the sample was loaded to 5 N for 60 min before sliding at 100 mm/s. After 30 min of sliding at 5N, sliding ceased and load was decreased to 0.1 N for 60 min to establish the "resting equilibrium" state for a nominally unloaded contact (see Figure 2A; 0–150 min).

Testing procedure and analysis

Following preconditioning, each sample was subjected to the five different equivalent daily activity regimens in a randomized order (see Figure 2A for representative sample and test protocol). Direct measurements of normal force, friction force, compression, and thickness

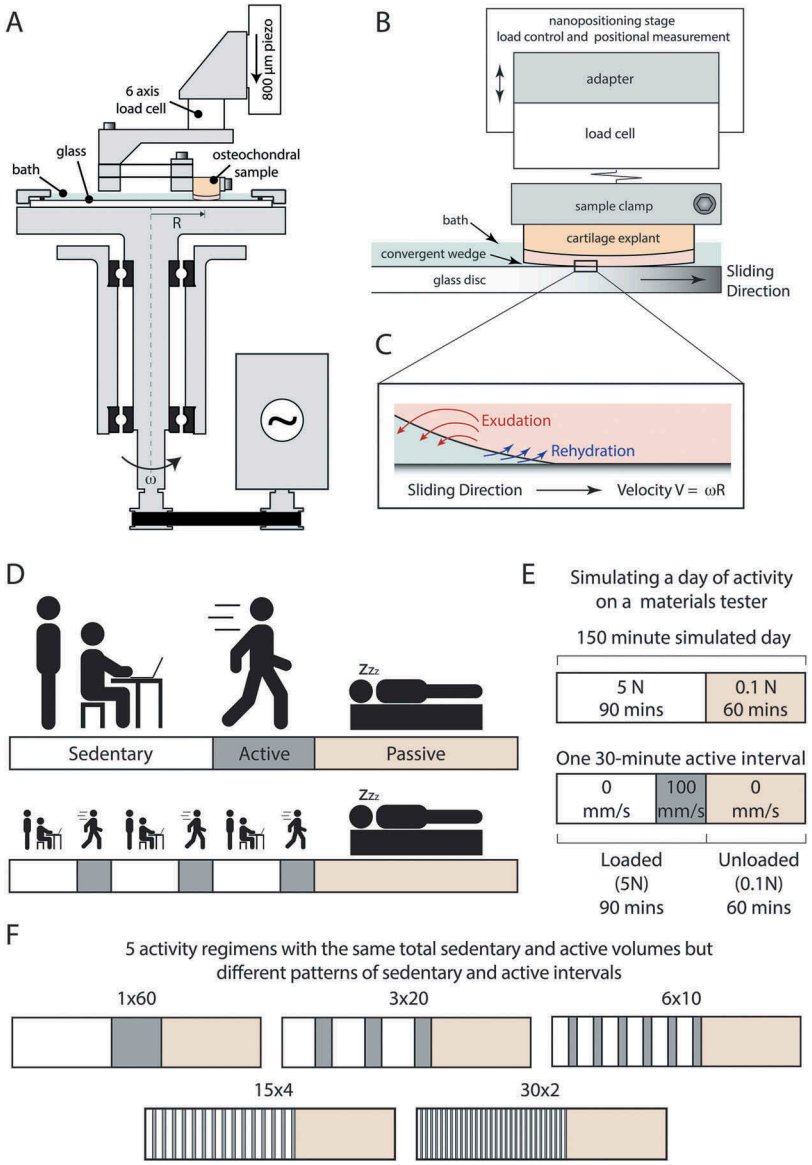

Figure 1. Schematic of the *in situ* pin-on-disk materials tester, the cSCA sliding environment, and the experimental protocol. (A) In the pin-on-disk materials testing device, a glass disk is attached to a stepper motor capable generating sliding speeds up to 100 mm/s. The osteochondral plug is pressed against this counterface while submerged in PBS plus protease inhibitors. (B) A 6-channel load cell records normal and friction forces and a piezo-driven actuator provides positional measurement. (C) The geometry of the cSCA configuration and its convergent wedge is believed to drive a net fluid inflow that restores cartilage hydration and thickness (i.e., tribological rehydration). (D) Patterns of activity vary over the course of a normal day as people work, move, and sleep. This was translated to a (E) 150-min equivalent 'day' based upon the relationship between contact areas and fluid exudation time scaling between benchtop and *in vivo* tests. Gray shading indicates when the sample was held under compressive load (5 N) and subjected to sliding at 100 mm/s; white boxes indicate the application of static compression (5 N) only; tan boxes indicate a bout of reduced static loading (0.1 N) to model unloading during sleep. This shading scheme is conserved throughout the paper. (F) Each sample underwent five separate activity regimens (in a randomized order); which are described in Supplemental Table S4.

were used to quantify a number of biomechanical outcomes including compressive strain, kinetic friction coefficient, contact radius, contact pressure, shear stress, effective modulus, interstitial pressure, and fluid load fraction. The assumptions and specific calculations underlying these assessments are provided in the Supplemental Material S.3 and in a prior paper.[16] Data were processed using a custom-written code in MATLAB (The MathWorks Inc, Natick, MA). Data for individual "equivalent days" (encompassing loading, sliding, and recovery) were extracted from each dataset; data from a representative 3 × 20 activity regimen (from Figure 2A) is shown in Figure 2(B–C). The starting and ending values from each active bout were used to

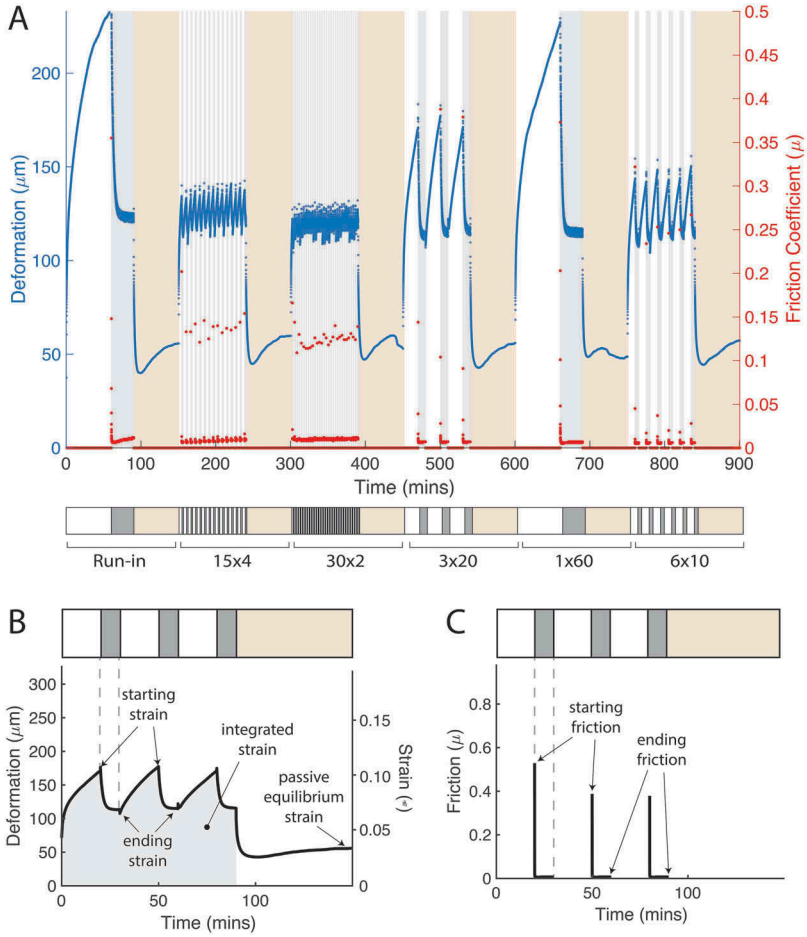

Figure 2. Data for a single representative sample (Sample 3) and its respective data analysis. (A) Deformation and friction data recorded from a sample subjected to each activity regimen, in a randomized order, after an initial run-in test (0–150 min). The traces from the 3 × 20 activity regimen in Panel A (centered around the 500 min mark) are broken out into separate figures for (B) deformation and strain, and (C) kinetic friction coefficient assessment. The value at the beginning of each sliding bout is taken to be the "starting" value, and the value during the last sliding cycle sliding in each bout is taken to be the "ending" value. Start deformation values were averaged together to yield a mean start deformation for each activity regimen. The same procedure is used to obtain mean ending deformation values. Similar starting and ending values can be calculated for strain, kinetic friction, interstitial pressure, etc. The shaded area indicates the region used to determine the time-averaged strain, as well as the time-averaged friction.

determine the mean and standard deviation for each biomechanical outcome. A linear mixed-effects (LME) model was used to fit the averaged starting/ending and time-averaged results as a function of activity regimen (fixed effect) while accounting for variance due to differences between explants (random effect) based upon sample-specific intercepts.

Results

The results shown in Figure 3, which were taken from sample #3 of 5, demonstrate load-induced exudation of interstitial fluid during "sedentary" bouts (5N + 0 mm/s), sliding-induced fluid recovery during "active" bouts (5N + 100 mm/s), and Donnan equilibrium-driven fluid recovery during the "passive" unloaded bout (0.1N + 0 mm/s). Predictable effects of interstitial fluid loss during each sedentary bout are well-illustrated in Figure 3; the contact pressure, interstitial pressure, effective modulus, and fluid load fraction decreased, while strain and contact radius increased. During each subsequent sliding bout, tribological rehydration-driven recovery of interstitial fluid led to a rescue of deformation and strain, interstitial pressure, effective modulus, fluid load fraction, kinetic friction coefficients, and shear stresses. Importantly, the composition of each individual activity regimen had a strong effect on start-of-sliding, but not end-of-sliding, biomechanical outcomes. For example, while 60 min of continuous inactivity led to massive losses of interstitial fluid, pressure, stiffness, and lubrication, these effects were virtually eliminated when the same amount of daily inactivity was distributed into 30 equally-spaced

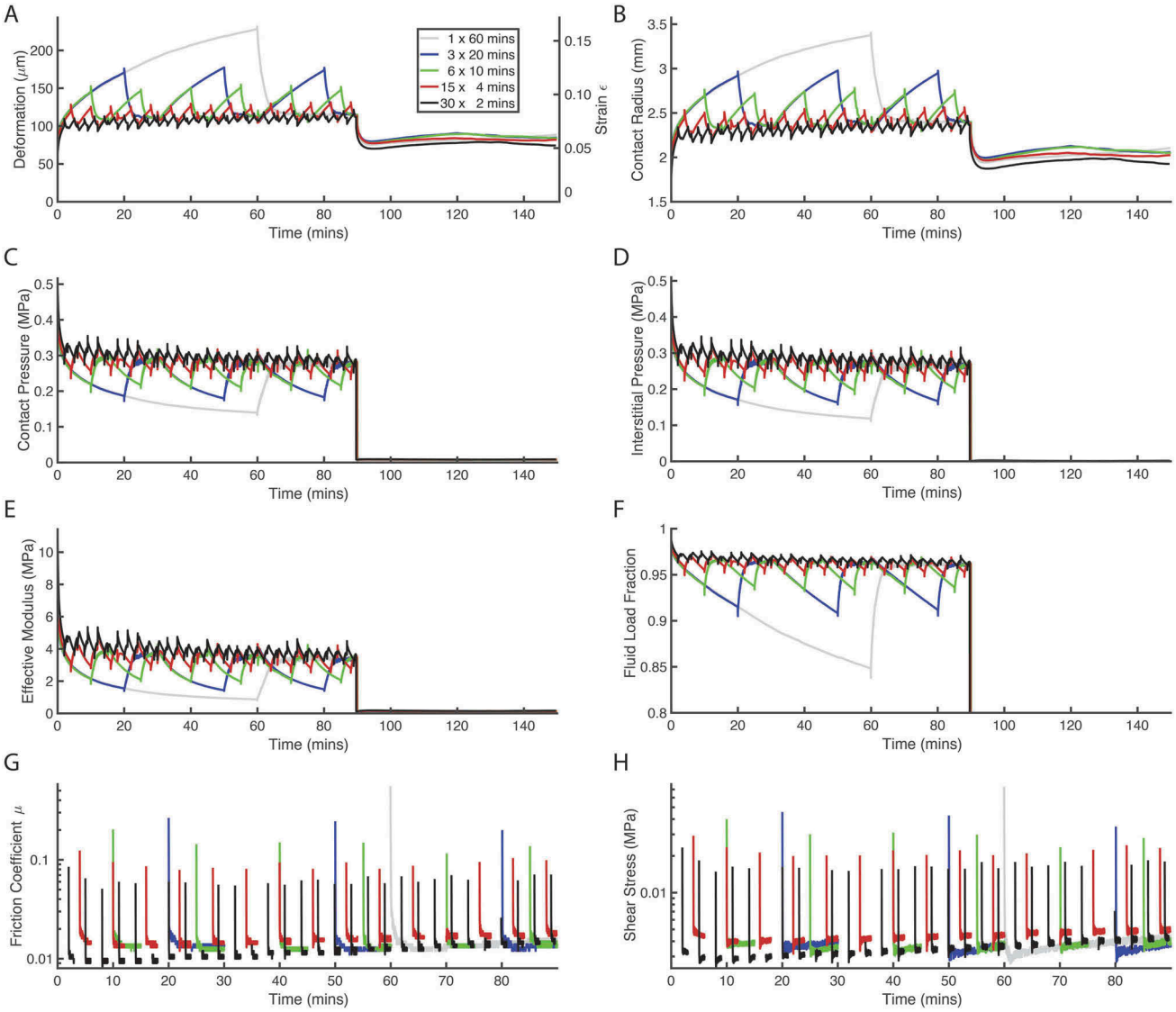

Figure 3. Overlaid parameter traces for all activity regimens for the representative sample shown in Figure 2A (Sample 3). (A) Deformation was measured directly, and strain calculated from post-hoc cartilage thickness measurements. (B) Contact radius is calculated from deformation, sample radius of curvature, and an assumed contact geometry. (C) Contact pressure was calculated from the measured normal force and contact radius. (D) Interstitial pressure, E) effective modulus, and (F) fluid load fraction were determined relative to the equilibrium modulus, calculated at equilibrium (defined as the end of the passive unloaded portion of each activity regimens). (G) Kinetic friction coefficient was measured and (H) shear stress determined from the friction force measurements and contact radius. For friction and shear stress, the passive portion of the experiment (90–150 min) was removed to improve visualization. Static loading, during the sedentary bouts, led to time-dependent increases in cartilage deformation and strain, and contact radii; and decreases in contact pressures, interstitial pressures, elastic moduli, and fluid support fraction. Activity (sliding) reversed these changes, with more-frequent activity cycles, and thus shorter sedentary bouts, markedly suppressing biomechanical changes when compared to less-frequent activity cycles. More-frequent activity bouts also suppressed detrimental increases in start-of-sliding kinetic friction coefficients and shear stresses.

2-min bouts (30 x 2 min). In each sample, end-of-sliding biomechanical values were consistent within and between activity regimens, reflecting a load and sliding speed-dependent biomechanical "dynamic equilibrium".[27,29] Individual samples also exhibited slight to no drift in their quasi-dynamic equilibrium values over time, as individual start- and end-of-sliding outcomes were consistent across each equally-spaced sedentary and active bout within an intermittent activity regimen.

Average start-of-sliding, end-of-sliding, and recovered -strain and -friction outcomes plotted as a function of sedentary bout length are shown in Figure 4 for the five different cSCA samples. Interestingly, despite relatively large inter-sample variability in strain and friction parameters ($p < 0.013$ to <0.001; see LME random [sample]

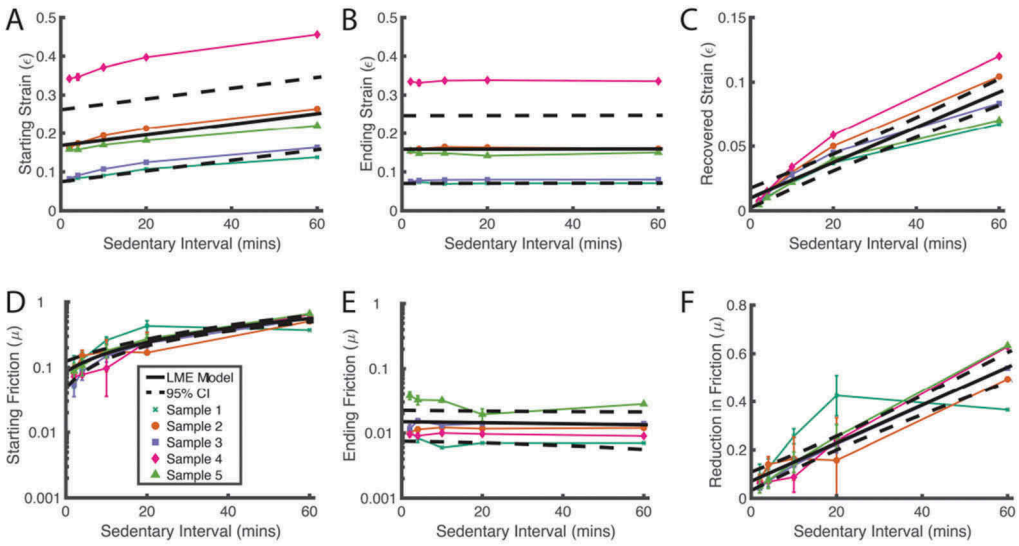

Figure 4. Biomechanical parameters plotted as a function of sedentary bout length: strain at (A) the start-of-sliding, (B) the end-of-sliding, and (C) recovered between the start- and end-of-sliding. Kinetic friction coefficients at (D) the start-of-sliding, (E) the end-of-sliding, and (F) reductions between the start- and end-of-sliding. Data points represent the mean ± standard deviation of the values recorded at the start-of-sliding (A,D), end-of-sliding (B,E), or mean of the difference between the start and end values (C,F) for each sample during a given activity regimen. There are no error bars for the 60-min bouts since only one start and end value were recorded per sample. Mean values (i.e., the data points shown) were used for the LME fit; the slope of the LME and the 95% confidence intervals shown. For a fixed total sedentary volume (60 min), start-of-sliding strain and friction increased significantly with increasing sedentary bout length, and thus less-frequent activity bouts. Sedentary bout length did not have a significant influence on end-of-sliding strain or friction, and as a result strain recovery and friction reduction was minimal for shorter sedentary bouts and more-frequent activity and was highest for longer sedentary bouts and less frequent sliding activity.

effect "intercept" analyses in Table 1 and Supplemental Table S5), the manner in which strain and friction changed in response to different sedentary bout lengths was statistically similar among samples. Overall, strains and frictions were significantly greater at the start of each sliding bout than at the end of each respective bout (Figure 4A vs. B, D vs. E). Start-of-sliding strain and start-of-sliding friction increased similarly and significantly across all samples as sedentary bout length grew (slope = $1.39\text{x}10^{-3}$units/min, $p < 0.001$ and 7.85×10^{-3}units/min, $p < 0.001$, respectively; see LME fixed [sedentary bout length] effect "slope" analyses in Table 1). However, individual sedentary bout length had no significant effect on end-of-sliding strain or end-of-sliding friction magnitudes (slope = 1.53×10^{-5}, $p = 0.605$ and -2.61×10^{-5}, $p = 0.386$, respectively; Table 1). This finding was consistent with the observation that sliding restored interstitial hydration to the same dynamic equilibrium across the entirety of individual explant tests regardless of sedentary bout length (Figure 3). Measures of recovered strain (i.e., tribological rehydration) and reduction in friction increased significantly and similarly in all samples with increasing sedentary bout length (slope = 1.37×10^{-3}, $p < 0.001$ and 7.87×10^{-3}, $p < 0.001$, respectively; Figure 4(C, F) and Table 1). In other words, while observed strain magnitudes varied among samples, presumably due to differences in material properties like aggregate modulus, the sliding-induced recovery of fluid and lubricity appeared largely insensitive to variations in material properties.

Table 1. LME model parameters for the analyses and fits shown in Figure 4. The coefficient for the fixed effect of sedentary bout length on each parameter (slope) is shown, the indicated p-value is derived from the F-Test for significance of this fixed effect on individual tribomechanical parameters. The intercept p-value evaluates the significance of the sample identify (random) effect on individual parameters.

	Effect of Sedentary Bout Length (Fixed Effect)		Effect of Sample Variability (Random Effect)
Parameter	*Slope (units/min)*	*p-value*	*Intercept p-value*
Starting Strain	1.39E-03	< 0.001	0.001
Ending Strain	1.53E-05	0.605	0.001
Starting Friction	7.85E-03	0.000	< 0.001
Ending Friction	−2.61E-05	0.386	< 0.001
Recovered Strain	1.37E-03	< 0.001	0.013
Reduction in Friction	7.87E-03	< 0.001	0.001

Figure 5 illustrates the effects of sedentary bout length on fluid load fraction, interstitial pressure, shear stress, and effective modulus at both the start- and end-of-sliding. Fluid load fraction, interstitial pressure, and effective modulus at the start-of-sliding all significantly decreased with increasing sedentary bout length (Figure 5(A, C, G); slope = -1.66×10^{-3}, -1.26×10^{-3}, and $-1.69\text{x}10^{-2}$units/min, respectively, $p \leq 0.001$ for

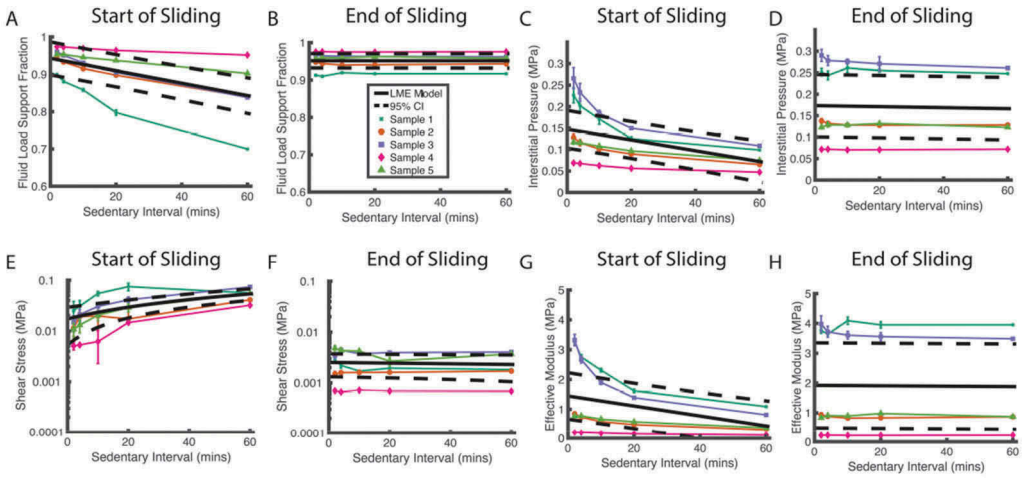

Figure 5. Calculated mechanical and tribological parameters plotted as a function of sedentary bout length during intermittent activity: fluid load support fraction at the (A) start- and (B) end-of-sliding, interstitial pressure at the (C) start- and (D) end-of-sliding, shear stress at the (E) start- and (F) end-of-sliding, and effective modulus at the (G) start- and (H) end-of-sliding. Data points represent the mean ± standard deviation of the values for each activity cycle. There are no error bars for the 60-min bout since only one start and end value was recorded per sample. In many cases, the errors bars are too small to be visualized behind the plotted marker. The slope of each LME and its 95% confidence interval are plotted overtop the data. For a fixed total volume of sedentary time (60 min), fluid load fraction, interstitial pressure, and effective modulus at the start-of-sliding decreased significantly as sedentary bouts lengthened, while start-of-sliding shear stress significantly increased with sedentary bout length. The length of individual sedentary bouts did not have an influence on end-of-sliding fluid load fraction, interstitial pressure, shear stress, or modulus.

each, Table S5), while shear stress increased significantly (Figure 5E; 6.08×10^{-4}units/min, $p < 0.001$, Table S5). Only ending interstitial pressure appeared to be influenced by sedentary bout length (Figure 5D; slope = $-1.18\text{x}10^{-4}$units/min, $p = 0.032$, Table S5). No other end-of-sliding outcome was influenced by sedentary bout length (Figure 5(B, F, H); slopes not significantly different from zero, Table S5).

The time-averaged strain, interstitial pressure, and friction coefficient, as well as accumulated time at high friction, are shown as functions of sedentary bout length in Figure 6. Time-averaged strain increased significantly with sedentary bout length (Figure 6A) while time-averaged interstitial pressure significantly decreased (Figure 6B). Even though starting friction increased with length of the sedentary bouts, no significant change in the time-averaged friction coefficient with increasing sedentary bout length was detected (Figure 6C). Because friction coefficients decreased rapidly, their effects were disproportionately biased by longer periods of very-low steady-state friction. However, when looking at the amount of time (or equivalently number of sliding cycles) spent above a given threshold friction value ($\mu > 0.1$ is shown in Figure 6D), increasing sedentary bout length led to significant increases in high-friction exposure (slope = 0.134, $p = 0.008$). Similar outcomes were observed when the friction threshold was set to $\mu > 0.05$ (data not shown). Supplemental Table S5 summarizes the statistics for the mixed effects models used to fit the data in Figures 5 and 6.

Discussion

While it is increasingly accepted that physical activity is a prerequisite for joint health and longevity, the mechanisms underlying these benefits, whether they are mechanical or biological in nature, and how they should be optimized, remain to be elucidated. Previously, we had shown that physical activity could enhance the biomechanical performance of articular cartilage explants through the articulation-mediated regulation of cartilage hydration; activity can drive the halting and recovery of interstitial fluid loss (which had been inferred *in vivo* and *ex vivo*),[19–21] helping to restore cartilage interstitial hydration and lubrication, and biomechanical function. However, studies investigating the influence of joint activity patterning, or regularity, on the biomechanical performance of articular cartilage have been lacking, due to substantial challenges in performing such studies in a well-controlled and physiologically-relevant manners.

The stationary contact area (SCA) explant testing configuration, consisting of a small (~6 mm ϕ) flat osteochondral explant mated against a flat sliding

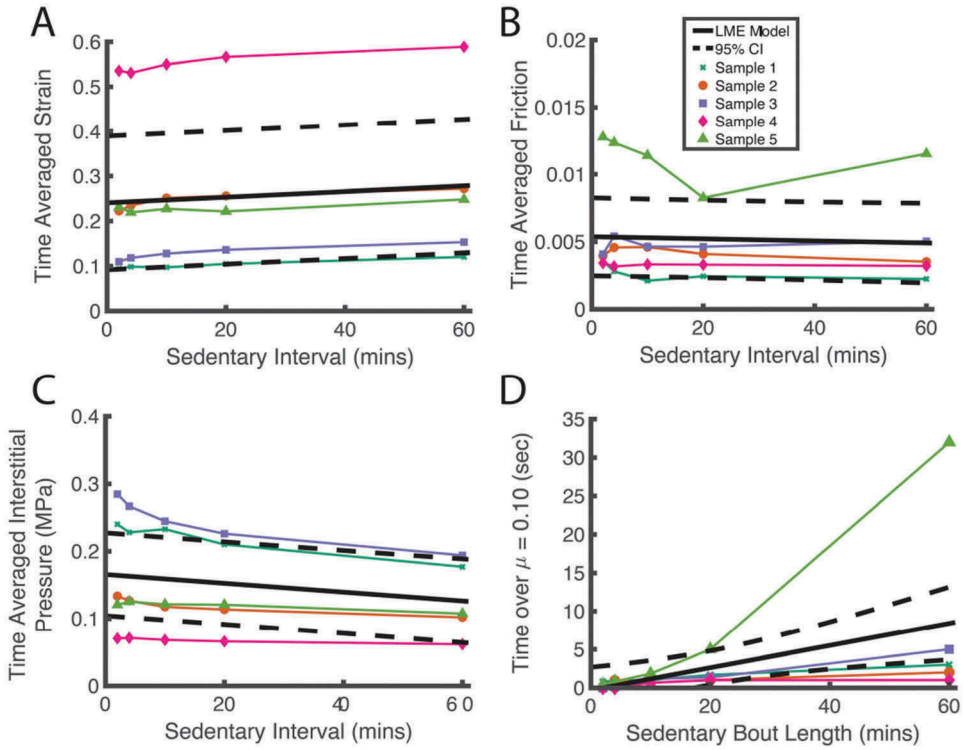

Figure 6. Time-averaged tribomechanical parameters plotted as a function of sedentary bout length: (A) time-averaged strain, (B) time-averaged interstitial pressure, (C) time-averaged friction coefficient, and (D) accumulated time at high-friction (μ > 0.01). For time-averaged data, each parameter was integrated over the entire "awake" portion of each regimen, then divided by the total-loaded time (90 min) to yield an average value for the activity regimen. The slopes of the LME and their 95% confidence interval are plotted overtop the data. When total sedentary time was fixed at 60 min, the length of individual sedentary bouts significantly influenced cartilages time-averaged strain, interstitial pressure, and time spent with friction coefficients >0.1, but not time-averaged friction.

countersurface, has been the most commonly utilized cartilage tribology testing configuration in the literature due to its excellent experimental control and measurement resolution. However, the SCA could not be utilized for this study i) because of its inability to recapitulate activity (sliding)-induced fluid recovery, as seen *in vivo*; and ii) its tendency to drive unmitigated and non-physiological levels of fluid exudation, interstitial fluid depressurization, and (high) frictional outcomes during sliding.[30] Similarly, use of the MCA configuration was precluded due to the fact that the tribomechanical response of the MCA is driven by contributions from contact migration (by definition),[39] bath exposure, and presumably, tribological rehydration; which cannot be disentangled.

Instead, because of its ability to allow for the careful titration, maintenance, and recovery of interstitial hydration, pressure, and lubrication (through a sliding-driven mechanism termed tribological rehydration)[27] and its ability to isolate the influence of sliding on cartilage mechanics from those contributed by other mechanisms, we turned to the newly re-discovered "convergent stationary contact area" (cSCA) explant testing configuration to study the relationships between aspects of activity patterning (intermittent sliding regimes), and articular cartilage hydration and function. Because of the cSCA's ability to competitively recover interstitial fluid in a sliding-dependent manner, the contact is unique in its capacity to restore and sustain interstitial lubrication under constant load, allowing the conduct of very-long-term tribology tests under extremely-low, and physiologically-consistent steady-state frictions (μ < 0.05).[28,30,40] By leveraging the control, resolution, and physiological-consistent outcomes afforded by the cSCA, we tested the hypothesis that for a given amount of "active" and "sedentary" volume in a "day", activity regularity, or equivalently, the length of continuous "sedentary" time spent between bouts of sliding, is a major determinant of articular cartilage tribomechanical outcomes. Our results indicated that, when controlling for total sedentary and active time (60 & 30 min, respectively), the frequency of intermittent activity (as measured by sedentary bout length) significantly affected the "daily" biomechanical envelopes that cSCA articular cartilage experienced. Starting from an initial-hydration state at resting equilibrium, static loading

caused cartilage to lose interstitial fluid and pressure; in agreement with bi-/multi-phasic cartilage theory.[16] However, upon initiating high-speed sliding, and without changing the magnitude of the applied load, fluid exudation in the cSCA was reversed and articular cartilage hydration, thickness, and biomechanical function were restored. Because exuded fluid volume increases with time under a given load, the detrimental biomechanical effects of inactivity increased with sedentary bout length; "less-frequently-active-cartilage" experienced larger tissue strains and lower interstitial pressures, higher peak/start sliding friction conditions, and increased number of high-friction sliding cycles when compared to "more-frequently-active-cartilage" explants. From a purely biomechanical standpoint, these *ex vivo* results suggest that shorter and more regular bouts of intermittent activity are likely preferred to longer and less regular bouts.

An important question to consider is whether our *ex vivo* findings have implications regarding *in vivo* joint biomechanics. Integrating prior *in vivo*/*in situ* findings with our cSCA studies suggests they can. Coleman et al. used MRI to assess changes in cartilage strain between 8 am and 4 pm, following a day of normal activity.[41] They found an accumulation of 3.1–5.1% and 1.9% strain in the tibial plateau and femoral condyles, respectively. An *in vivo* MRI study of the knee by Eckstein et al., which is more comparable to our work, tested the effect of intermittent knee bends on cartilage compression.[42] Following 50 and 100 knee bends, cartilage thinned by 2.4–8.6% and 2.4–8.5%, respectively, compared to the before-exercise value. Intriguingly, if one subtracts the initial resting equilibrium strains from our end-of-active-period strains, we see "diurnal" strain variances of 2–7% (Figure 7), in good quantitative agreement with the measurements from Coleman et al. and Eckstein et al. Eckstein's observation that strains after 100 knee bends were no different from strains after 50 knee bends, nor following up to 11 subsequent sets of 50 knee bends with 15-min rest periods between sets, is also consistent with our observation that similar "dynamic strain equilibria" were attained after 1, 2, 5, 10, or 30 min of sliding and were unaffected by subsequent activity bouts. These comparisons suggest that the results of this study can be extended with reasonable confidence to a more general understanding of joint activity and biomechanics.

All *ex vivo* cartilage explant testing models have drawbacks, and despite the high degree of experimental control afforded by the cSCA configuration and its ability to drive physiologically-consistent tribomechanical outcomes, this study does have notable limitations. Admittedly, the cSCA and our loading environment, consisting of cartilage statically compressed and slid unidirectionally against a flat glass counterface, cannot recapitulate the full mechanical environment the cartilage experiences. *In vivo*, unidirectional articulation is impossible, instead, cartilage experiences reciprocal sliding, or sliding reversals, during gait. Prior studies from our team have investigated the influence of reciprocal and uni-directional sliding on cSCA tribomechanics;[27–31] indeed, one of these reciprocal sliding studies hinted at the ability of intermittent activity to modulate cartilage strain and friction behaviors, motivating the current study.[29] Together, our past and present observations highlight the qualitatively similar responses of cSCA cartilage to intermittent activity under both reciprocal and uni-directional sliding.

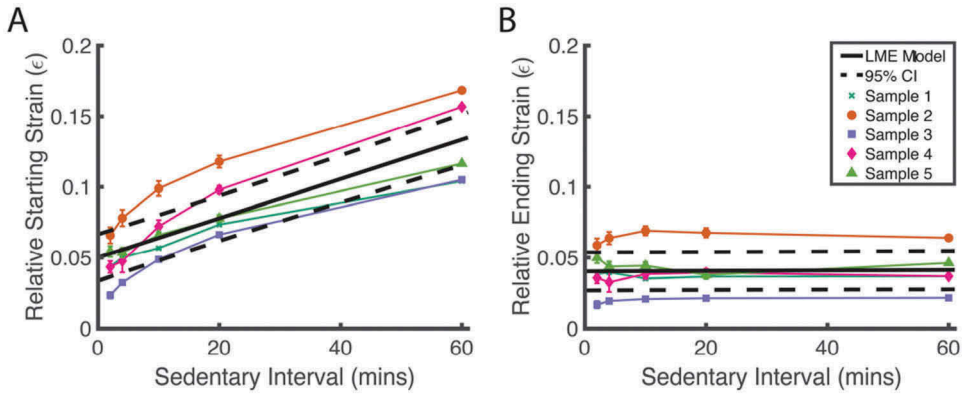

Figure 7. Strain at the (A) start- and (B) end-of-sliding measured relative to the average passive equilibrium strain (recorded the end of the passive "overnight" period) for each sample. Mean ± standard deviation for relative strain is plotted for each sample and activity regimen; there are no error bars for the 60-min bout since only one start and end value was recorded per sample. LME slopes and their 95% confidence intervals are plotted overtop the data. The use of relative strain makes for better comparisons to *in vivo* measurements where the initial reference condition is often still loaded, though either briefly or at a low magnitude. The range of the relative strains generated here overlaps those seen in *in vivo* studies by Coleman et al. and Eckstein et al.

In vivo, cartilage is subject to loading/unloading during the gait cycle. However, loading/unloading was explicitly avoided in the present study because such dynamic behavior allows for fluid transport via non-sliding-driven phenomena, including "pumping" via cyclic loading/unloading and bath exposure. The cSCA is an ideal setup for isolating the contributions of purely-sliding-driven phenomena in the modulation of cartilage hydration and tribomechanics; it is the only testing configuration that promotes sliding-driven hydrodynamic interfacial phenomena and the ability to controllably rehydrate the tissue while eliminating/minimizing contributions from contact migration, bath exposure, and cyclic loading/unloading. Such an approach necessitated the use of constant compressive stresses during the "active" portion of the day, and we settled on the application of a stress of ~0.2 MPa, which represented a compromise between the average contact stresses experienced by cartilage during two-legged stance (~0.2 MPa)[35] versus gait (up to 1 MPa).[36]

It is reasonable to suspect that sliding in the presence of PBS could artificially increase frictional outcomes; however, it should be noted that the mean dynamic equilibrium friction coefficient seen during cSCA tests with PBS is exceptionally low (~0.01), and comparable to those reported for synovial fluid and saline-lubricated dog ankles (0.006 and 0.012, respectively).[20] This is due to the fact that the cSCA, unlike other stationary contact configurations, actively replenishes and sustains high-levels of interstitial lubrication during sliding. Nonetheless, our results did reveal the presence of very-high transient friction coefficients following even modest sedentary bouts. By definition, boundary lubricants, such as those in synovial fluid, help protect surfaces under the most extreme tribological conditions; thus, we posit that a primary function of boundary lubricants in synovial fluid may be friction and damage mitigation during "start-up cycles" where interstitial lubrication is the most compromised. The present study also only focused on the effects of activity bout frequency for a single constant contact stress (~0.2 MPa) and volume of activity (30 min). Studies investigating the effects of lubricant supplementation, contact pressure, surface geometry, tissue composition, total activity volume, reciprocal sliding, and gait-mimicking loading/unloading on tribological rehydration and cartilage biomechanics are points of focus of future investigations.

The connections between this explant study's outcomes and aspects of *in vivo* cartilage behavior present an opportunity to speculate about links between exercise, inactivity, cartilage degradation, and joint health. The most obvious connection involves wear; physical mechanical damage is least likely when sliding prevents the excessive loss of interstitial hydration and lubrication. The same can be said for cell-mediated biochemical damage of cartilage, which tends to correlate positively with shear stress and negatively with interstitial pressure.[43–53] While it is intuitive that exercise might promote the "wear and tear" of joint surfaces, which are bearings after all, the present study highlights an alternative interpretation; that joint activity associated with exercise has the potential to directly reverse load-induced compromise of cartilage biomechanics and lubrication. Because the biomechanical functions of cartilage are highly-dependent on hydration state, patterning of activity (in this case intermittent sliding) that prevents/limits/recovers excessive cartilage dehydration may help in maintaining biomechanical functions necessary to mitigate both biomechanical and biological (cell-mediated) causes of cartilage dysfunction (e.g., reduced peak and accumulated cartilage strains and shears). Furthermore, the present findings represent a benchmark from which to explore how titration of activity volume and activity patterns can be used to influence the mechanobiological response of cartilage, and regulate the longevity of healthy, injured, and diseased joints.

It should be noted that natural joint articulation allows for numerous cartilage rehydration mechanisms to be engaged simultaneously (e.g., bath exposure and Donnan equilibrium-driven fluid recovery, dynamic loading-unloading driven pumping, tribological rehydration, etc.). Therefore, the activity-driven recovery dynamics reported herein represent something of an "extreme" case scenario and may be treated as lower limits. Furthermore, while this study leveraged the cSCA's unique ability to drive tribological rehydration in order to investigate activity-hydration relationships on the benchtop, the modulation of cartilage hydration and tribomechanical behavior by activity is not predicated, *per se*, on the presence of tribological rehydration *in vivo*. Any mechanism that facilitates articulation-mediated rehydration of articular cartilage could promote an activity-dependent and beneficial recovery of interstitial hydration, pressure, and lubrication, and thus cartilage function; such is the amazing complexity of articular cartilage.

Lastly, while our results demonstrate a means by which exercise/activity can directly benefit the biomechanical properties of cartilage; optimal levels of activity necessary to prevent the biomechanical problems of excessive exudation *ex vivo* and *in vivo* remain unknown. An epidemiological study by Williams provided evidence that exercise helps prevent joint disease down to a relatively small level of activity, which they attributed not to an inherent benefit from activity, but to the detrimental effects of excessive inactivity;[13] an interpretation

consistent with our findings. Historical evidence also suggests that OA risk is higher in modern times even after controlling for obesity and increased lifespan.[1] The present findings provide a tempting, if not paradigm-shifting explanation for these observations, one rooted in modern sociodemographic shifts toward increasingly sedentary and inactive lifestyles. Sedentary bouts drive cartilage dehydration and potentially detrimental tribomechanical conditions when articulation is initiated, conditions that are exacerbated by prolonging sedentary bout length. Unfortunately, our results also hint at the possibility that the detrimental effects of a long sedentary period may not be best undone by a single, long post-sedentary activity. In more practical terms, after scaling exudation times to account for *in vivo* cartilage contact sizes, the results hint that shorter and more regular activity bouts (e.g., every 30 min to 1 h) may help mitigate exudation and loss of tissue function *in vivo*. Such findings can begin to provide new mechanistic understandings of the non-intuitive relationships between moderate exercise, improved joint health, and reduced OA risk,[8,13] as well as support and strengthen recent assertions that drastic, post-industrial increases in OA prevalence in developed countries, like the United States, might be best explained by changes in lifestyle reflecting increased sedentariness and altered activity patterning.[1] However, further *ex vivo* and *in vivo* studies are needed before recommendations regarding activity patterning can be made, but it is worth noting that this interpretation is consistent with broader findings encompassing seemingly unrelated diseases (e.g., cardiovascular disease) and all-cause mortality.[4,25]

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Disclosure statement

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