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Association of Low Physical Activity Levels With Gait Patterns Considered at Risk for Clinical Knee Osteoarthritis Progression

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Objective. Although gait analysis provides an estimate of joint loading magnitude and patterns during a typical step, accelerometry provides information about loading frequency. Understanding the relationships between these components of loading and knee osteoarthritis (OA) progression may improve conservative management, as gait interventions may need to account for physical activity levels or vice versa. The primary objective was to examine relationships between gait patterns that have previously been associated with OA progression and accelerometer-derived metrics of loading frequency. The secondary objective examined the association of accelerometer-derived metrics and total knee arthroplasty (TKA) at a mean follow-up of 3.5 years.

Methods. Fifty-seven individuals with knee OA underwent gait analysis and 1 week of accelerometer wear. Spearman correlations were calculated between accelerometer-derived metrics and gait patterns. Differences across quartiles of step count were examined with Jonckheere-Terpstra tests. In a subsample, baseline differences between TKA and no TKA groups were examined with Mann-Whitney U-tests.

Results. Gait variables previously related to progression were correlated to both step count and moderate- to vigorous-intensity, but not lower-intensity, physical activity. Individuals in the lowest quartile (~4000 steps/day) exhibited gait patterns previously related to progression. There were no differences in any baseline accelerometer-derived metrics between those that did and did not undergo TKA at follow-up.

Conclusion. Complex relationships exist between gait, physical activity, and OA progression. Accelerometer-derived metrics may contribute unique information about overall loading for individuals above a certain activity threshold, but for those with lower activity levels, gait may be sufficient to predict clinical progression risk, at least over the short term.

INTRODUCTION

Mechanical loading has been implicated as a key factor in osteoarthritis (OA) (1,2). Gait analysis in individuals with knee OA has demonstrated that baseline joint moments and electromyography are associated with both longitudinal structural joint changes (3–11) and future total knee arthroplasty (TKA) (4,12–14), which is considered the clinical endpoint for OA. These gait data describe time-varying features of joint loading during a typical step but do not provide information about how often the joint encounters these loads during daily life or whether all steps are "typical" (ie, the frequency components of joint loading). Understanding the role of joint loading frequency in OA progression has the potential to improve conservative OA management by concurrently optimizing gait patterns and physical activity.

The combined influence of gait patterns and joint loading frequency, termed "cumulative load" (15), has only recently been explored (5). Brisson et al used a surrogate physical activity measure derived from accelerometer data, step count, to examine the additional contribution of joint loading frequency to explain structural disease progression and found that adding step count to a model containing baseline knee adduction moment (KAM) impulse did not explain more variance in 2.5-year cartilage volume change (5). Although these results

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suggest that joint loading frequency did not contribute valuable information about progression risk, the potential contribution of joint loading frequency to clinical knee OA outcomes, such as TKA, has not been explored and may differ from structural outcomes given prior research showing that different baseline gait patterns were associated with structural versus clinical (TKA outcome) knee OA progression (4). Furthermore, it is unclear whether measures of the intensity of physical activity could contribute additional value. Integrating joint loading frequency information into a measure of cumulative load or a statistical model of OA progression will only be useful for predicting progression if these measures capture a domain that is distinct from the information captured by gait metrics.

Physical activity has been shown to improve clinical OA symptoms such as pain (16) and is recommended in OA guidelines as a core management component (17); however, higher step count has also been associated with higher pain, explaining an additional 9% variance in pain after accounting for body mass index (BMI), knee extensor strength, and KAM impulse (18). Taken together, these results suggest a complex relationship between gait, joint loading frequency, and clinical OA outcomes, such that joint loading frequency may provide additional value. Furthermore, an acute bout of physical activity (20 minutes of treadmill walking) has been associated with increased pain and corresponding gait changes in some, but not all, individuals with knee OA (19), and baseline knee-specific gait features have been associated with increased pain following a 6-minute walk test (20). Both findings suggest that specific combinations of gait patterns and physical activity may affect OA symptoms and individuals may modulate their activity based on gait. Although these bouts likely represent moderate- to vigorous-intensity physical activity (MVPA), lower-intensity physical activity and sedentary behavior (SED) may also be relevant to clinical outcomes, as time spent in light-intensity physical activity (LPA) has been associated with reduced risk of onset and progression of disability (21). Also, replacing sedentary time with LPA has been associated with reduced risk for incident slow gait speed (22) in those with or at risk of knee OA without baseline disability.

In order to gain insight into whether joint loading frequency measures provide additional information that may be useful for understanding clinical knee OA progression, the primary objective of this study was to examine the relationships between features of knee moments and electromyography patterns during gait that have previously been associated with a clinical knee OA outcome (TKA) and both step count and intensity metrics derived from physical activity data. We hypothesized that lower step count would be significantly correlated with gait metrics that have previously been associated with TKA but that intensity metrics would have fewer significant correlations (ie, intensity-based accelerometer data, particularly LPA, would provide information about the overall joint loading exposure that was independent of that provided by gait). Our secondary objective was to compare baseline accelerometer metrics between those who did and those who did not reach a clinical OA progression outcome (TKA) at a mean follow-up of 3.5 years in a subsample with available follow-up data to further assess whether these metrics were independently associated with TKA.

PATIENTS AND METHODS

Study overview and participants. As part of two ongoing longitudinal studies of gait and knee OA progression (9,12), 57 individuals with medial compartment knee OA participated in a gait data collection session between 2012 and 2015 and wore an accelerometer for 1 week following gait data collection. All participants were diagnosed with knee OA by a single high-volume orthopedic surgeon using clinical and radiographic criteria (23) and had both medial knee pain and medial tibiofemoral joint space narrowing greater than or equal to lateral joint space narrowing (24). Exclusion criteria included any cardiovascular, neuromuscular, or musculoskeletal conditions other than knee OA that would affect gait or participant safety during testing; age under 35 years; and having undergone or being on a waitlist for TKA or high tibial osteotomy. This research was carried out in accordance with the Helsinki Declaration, and all participants signed Nova Scotia Health Authority Research Ethics Board–approved informed consent forms prior to participation.

Kinematics, kinetics, and electromyography. Standardized protocols were employed to capture three-dimensional (3D) limb motion, ground reaction force data, and electromyography (25,26) during self-selected speed over-ground walking for the OA leg. Briefly, 3D motion data were collected at 100 Hz (Optotrack, Northern Digital) and synchronized with 3D ground reaction forces from a force platform embedded in the floor (model BP400600; Advanced Medical Technology) and electromyography (EMG) from seven muscle sites surrounding the knee joint (AMT-8 EMG; Bortec) digitized at 2000 Hz. Muscle sites included lateral gastrocnemius (LG) and medial gastrocnemius (MG), vastus lateralis (VL), vastus medialis (VM), rectus femoris (RF), biceps femoris (lateral hamstrings [LH]), and semimembranosus (medial hamstrings [MH]). Four to seven trials were retained for analysis.

Kinematics and kinetics were calculated using custom-written MATLAB programs (Mathworks) (25). In brief, 3D joint angles were calculated from 3D diode positions using a least-squares optimization routine (27) and expressed in the joint coordinate system (28). The 3D net external joint moments were calculated using inverse dynamics, time normalized to the stance phase of the gait cycle, and amplitude-normalized to body mass (29–32). EMG data were processed in MATLAB according to standardized protocols (26), where raw signals were corrected for bias, converted to μV, full-wave rectified, low pass filtered at 6 Hz using a Butterworth filter, and then time-normalized to the full gait cycle.

Muscle strength and EMG amplitude normalization. Following gait data collection, eight maximum voluntary isometric contractions (MVICs) were performed using standardized protocols (26,33) for the purposes of EMG amplitude normalization and strength assessment. In brief, the eight exercises were the following: *1*) plantar flexion in long sitting position, *2*) single leg standing heel raise with manual resistance applied to the shoulders, *3*) knee extension in sitting position (knee at 45° flexion), *4*) knee extension in sitting position (knee at 45° flexion) with simultaneous hip flexion (hip at approximately 90° flexion), *5*) knee extension in supine position (knee at 15° flexion), *6*) knee flexion in sitting position (knee at 55° flexion), *7*) knee flexion in supine position (knee at 15° flexion), and *8*) knee flexion in prone position (knee at 55° flexion). EMG waveforms for each muscle were amplitude-normalized to the highest activation amplitude (based on a 0.1-second moving window) of the same muscle during the MVICs (%MVIC) (26). A Cybex dynamometer (Lumex) was used to record torque data simultaneously with EMG data. For each muscle group, the highest amplitude steady-state 0.5-second window was identified (26) and normalized to body mass to calculate strength for each muscle group (Nm/kg).

Waveform feature extraction. Principal component analysis was used to extract major patterns of variation in the moment and EMG waveforms (principal components [PCs]) (26,34) from a larger dataset from individuals with and without knee OA in the Dynamics of Human Motion laboratory database (n = 428; 48% female; age: 55.2 ± 9.4 years; mass: 84.3 ± 18.3 kg; BMI: 28.8 ± 5.3 kg/m^2; gait speed: 1.29 ± 0.20; Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] total: 17.5 ± 18.8; Kellgren-Lawrence [KL] grade: 25 KL grade 1, 138 KL grade 2, 101 KL grade 3, and 46 KL grade 4). PCs extracted from a larger dataset are considered more robust and generalizable (35). In this larger dataset, two to four PCs cumulatively explained 90% of the variability among waveforms. This list was narrowed to only those PCs previously related to clinical OA progression, including overall KAM magnitude (PC1) (12); the difference between early-and midstance KAM (PC2) (12); early-stance knee flexion moment (KFM) magnitude (PC1) (12); the difference between early-stance KFM and late-stance knee extension moment (KEM) (PC2) (12); the difference between early-stance internal and late-stance external KRM (PC1) (9); internal KRM magnitude through midstance

Table 1. Sample characteristics for full study sample and across quartiles of step count

	Full sample, n = 57	Quartile 1, n = 15	Quartile 2, n = 14	Quartile 3 (n = 14)	Quartile 4, n = 14	*P* Value[a]	Pairwise Differences
Sex, female: male, n (% female)	20:37 (35)	8:7 (53)	7:8 (50)	3:11 (21)	2:12 (14)	0.06	
Age, mean ± SD, y	62.1 ± 6.9	66.5 ± 8.0	58.1 ± 4.9	60.5 ± 6.6	63.1 ± 4.7	0.64	
Mass, mean ± SD, kg	89.9 ± 17.1	96.3 ± 19.7	81.2 ± 18.9	91.0 ± 12.8	90.8 ± 13.8	0.81	
BMI, mean ± SD, kg/m^2	31.0 ± 5.5	34.8 ± 7.0	28.0 ± 4.3	30.9 ± 4.2	30.3 ± 3.6	0.35	
Gait speed, mean ± SD, m/s	1.26 ± 0.20	1.18 ± 0.15	1.29 ± 0.24	1.22 ± 0.19	1.35 ± 0.17	0.07	
Radiographic scores, n[b]							
KL grade (1, 2, 3, 4)	0, 10, 28, 16	0, 0, 8, 6	0, 3, 4, 6	0, 3, 8, 3	0, 4, 8, 1	0.01*	1 v 3,4
mJSN (0, 1, 2, 3)	1, 11, 28, 14	0, 1, 8, 5	1, 2, 4, 6	0, 4, 8, 2	0, 4, 8, 1	0.03*	1 v 3,4
latJSN (0, 1, 2, 3)	23, 22, 7, 2	3, 8, 3, 0	8, 3, 0, 2	5, 7, 2, 0	7, 4, 2, 0	0.27	
PF JSN (0, 1, 2, 3)	4, 30, 16, 4	0, 8, 5, 1	3, 5, 3, 2	0, 8, 6, 0	1, 9, 2, 1	0.41	
WOMAC scores, mean ± SD							
Pain (/20)	3.7 ± 3.7	4.3 ± 3.6	4.8 ± 4.4	4.3 ± 3.8	1.5 ± 1.7	0.05*	1,2,3 v 4
Stiffness (/8)	1.8 ± 1.6	1.7 ± 1.4	2.3 ± 1.9	1.8 ± 1.6	1.4 ± 1.3	0.39	
Function (/68)	12.3 ± 11.4	13.1 ± 9.6	15.2 ± 16.4	13.1 ± 11.2	7.6 ± 5.6	0.24	
Strength, mean ± SD, Nm/kg[c]							
Knee extensor	1.29 ± 0.37	0.99 ± 0.29	1.35 ± 0.28	1.38 ± 0.33	1.44 ± 0.41	<0.01*	1 v 2,3,4
Knee flexor	0.69 ± 0.22	0.55 ± 0.17	0.78 ± 0.17	0.65 ± 0.21	0.78 ± 0.24	0.08	
Plantar flexor	0.96 ± 0.33	0.73 ± 0.28	1.10 ± 0.32	1.02 ± 0.33	0.97 ± 0.31	0.12	
Physical activity data, mean ± SD							
Step count, steps/d	6697 ± 2367	3915 ± 668	5641 ± 641	7646 ± 383	9784 ± 1316	<0.01*	1 v 2 v 3 v 4
MVPA, % daily wear time	2.8 ± 1.8	1.1 ± 0.7	2.6 ± 0.9	2.7 ± 1.2	4.8 ± 1.9	<0.01*	1 v 2,3 v 4
MVPA, min/d	24 ± 16	9 ± 6	21 ± 7	25 ± 11	41 ± 16		
LPA, % daily wear time	33.2 ± 8.9	26.8 ± 6.7	30.4 ± 5.9	36.6 ± 7.8	39.5 ± 9.2	<0.01*	1,2 v 3,4
LPA, min/d	283 ± 78	221 ± 49	254 ± 55	324 ± 52	337 ± 86		
SED, % daily wear time	64.0 ± 9.3	72.1 ± 6.5	67.0 ± 5.7	60.7 ± 6.9	55.7 ± 8.5	<0.01*	1 v 2 v 3 v 4
SED, min/d	547 ± 98	606 ± 106	560 ± 77	546 ± 92	473 ± 70		

Abbreviation: BMI, body mass index; KL, Kellgren-Lawrence; latJSN, lateral joint space narrowing; LPA, light-intensity physical activity; mJSN, medial joint space narrowing; MVPA, moderate- to vigorous-intensity physical activity; PF JSN, patellofemoral joint space narrowing; SED, sedentary behavior; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

[a] Jonckheere-Terpstra test for ordered alternatives used to compare across quartiles, except for sex, for which a χ^2 test was used.

[b] Radiographic data were unavailable for n = 1 in Quartile 1, n = 1 in Quartile 2, and n = 1 in Quartile 4.

[c] Strength data were unavailable for n = 2 in Quartile 1, n = 2 in Quartile 3, and n = 1 in Quartile 4.

* Significant at $P < 0.05$.

(PC2) (36); overall activation of gastrocnemii, quadriceps, and hamstrings (PC1) (13); and prolonged quadriceps and hamstrings activation (PC2) (13). The retained moment and EMG PCs had intraclass correlation coefficients ranging from 0.70 to 0.94 (37) and from 0.73 to 0.98 (38), respectively. PC scores for all participants in the current study were calculated for each ensemble average waveform (across trials) by multiplying the waveform by each retained PC.

Accelerometer data collection and analysis. For 7 days following gait data collection, participants wore an ActiGraph GT3X+ tri-axial accelerometer (ActiGraph) on a waist belt approximately over the anterior superior iliac spine of the OA leg (39). Participants were instructed to wear the accelerometer during all waking hours except during water-based activities. A demonstration, a diagram, and written instructions of appropriate accelerometer placement were provided at the time of gait testing. Participants also kept daily written logs to record hours of accelerometer wear and activity participation.

Accelerometer data were resampled from 30 Hz to 1-minute epochs within ActiLife (ActiGraph) and transformed into units of counts/minute (CPM), a composite metric describing the frequency and intensity of acceleration. Wear time validation was performed using nonwear criteria of 90 minutes of zero activity with a 2-minute nonzero spike tolerance (40) in line with recommendations for individuals with knee OA (41). This analysis was compared with written activity logs to assess validity. Data for two participants (one female and one male), who reported wearing the accelerometer but engaging in mostly SED, were reprocessed without the wear time criteria to include these data as valid wear (visual data inspection confirmed some activity during the reported times). All participants in the current study wore the accelerometer for at least 4 days with at least 10 hours/day of valid wear time (40).

The average daily step count (steps/day) over the week of accelerometer wear was calculated with ActiLife's proprietary formulas. Each minute of valid data was categorized by intensity level using the following standardized cut-points (42): MVPA (1952+ CPM), LPA (100-1951 CPM), and SED (0-99 CPM). Daily MVPA, LPA, and SED were averaged over the week of accelerometer wear and expressed as a percentage of total wear time to account for the variability in wear time among participants and provide estimates of habitual physical activity levels (43,44).

Follow-up regarding surgical status. Participants were contacted by phone or email between 2015 and 2017 if they were at a minimum of 2.5 years past their gait testing session, and participants were asked whether they had undergone or were

Table 2. Spearman correlations (ρ) between physical activity and gait variables in individuals with medial knee OA

PCs		Interpretation	Step Count	SED (%)	LPA (%)	MVPA (%)
Moment (n = 57)						
KAM	1	Overall shape and greater magnitude	0.01	0.14	−0.15	0.10
	2	Greater early-stance, midstance difference	0.31*	−0.09	0.04	0.33*
KFM	1	Greater early-stance flexion moment magnitude	0.27*	0.02	−0.06	0.28*
	2	Greater early-stance flexion, late-stance extension difference	0.42*	−0.22	0.14	0.42*
KRM	1	Greater external, internal rotation moment difference	0.33*	0.01	−0.05	0.36*
	2	Greater midstance internal rotation moment magnitude	−0.02	0.08	−0.10	0.03
EMG (n = 52)						
LG	1	Overall shape and greater magnitude	−0.06	0.13	−0.13	−0.01
MG	1	Overall shape and greater magnitude	0.02	0.00	0.03	−0.10
VL	1	Overall shape and greater magnitude	−0.19	−0.07	0.11	−0.13
VM	1	Overall shape and greater magnitude	−0.21	−0.08	0.15	−0.25
RF	1	Overall shape and greater magnitude	−0.23	−0.15	0.23	−0.23
LH	1	Overall shape and greater magnitude	−0.19	0.08	−0.04	−0.11
MH	1	Overall shape and greater magnitude	−0.30*	0.10	−0.01	−0.36*
VL	2	Prolonged midstance activation	−0.33*	0.05	0.05	−0.25
VM	2	Prolonged midstance activation	−0.35*	0.07	0.00	−0.20
RF	2	Prolonged midstance activation	−0.36*	0.13	−0.06	−0.26
LH	2	Prolonged midstance activation	−0.42*	0.25	−0.17	−0.28*
MH	2	Prolonged midstance activation	−0.22	0.12	−0.06	−0.19

Abbreviation: EMG, electromyography; KAM, knee adduction moment; KFM, knee flexion moment; KRM, knee rotation moment; LG, lateral gastrocnemius; LH, lateral hamstrings; LPA, light-intensity physical activity; MG, medial gastrocnemius; MH, medial hamstrings; MVPA, moderate- to vigorous-intensity physical activity; OA, osteoarthritis; PC, principal component; RF, rectus femoris; SED, sedentary behavior; VL, vastus lateralis; VM, vastus medialis.
* Significant at $P < 0.05$.

scheduled for any lower-extremity surgeries since their previous testing sessions. Three were not yet past the 2.5-year minimum follow-up time, two did not respond to contact attempts, two had contact information that was no longer valid, one was deceased, and the remaining 49 provided follow-up data. Two participants had undergone contralateral TKA, and one had undergone ipsilateral total hip arthroplasty. Ten participants had undergone or were on a waitlist for TKA of the tested OA knee, and 36 had not had surgery. For those reporting TKA, time to TKA was used as time to follow-up. For all others, time to follow-up contact by the study team was used. This resulted in a mean time to follow-up of 3.5 ± 0.9 years.

Statistical analysis. Spearman correlation coefficients were calculated between accelerometer-derived variables (step count, MVPA, LPA, and SED) and PC scores for gait variables associated with progression using data from the full sample (n = 57). To further examine the relationship between physical activity and gait, the sample was divided into four quartiles by step count, and Jonckheere-Terpstra tests for ordered alternatives were used to compare demographics, clinical data, gait, and physical activity across quartiles.

Data from the subsample of individuals with follow-up surgical status available (with no surgeries to other lower-limb joints) were used to investigate baseline differences related to clinical progression (TKA). Further inspection of individuals meeting the above criteria revealed that all who had undergone/were on a waitlist for TKA had a baseline KL grade greater than 2, whereas those who had not undergone/were not on a waitlist for TKA included 10 participants with a KL grade of 2 and three participants without radiographic data available. To reduce potential confounding effects of baseline radiographic differences between groups, the no TKA group was limited to individuals with KL grades greater than 2, although a sensitivity analysis including all individuals was also performed. χ^2 tests and Mann-Whitney U-tests examined between-group differences in sex and ordinal radiographic scores, respectively. Because of the small groups and skewed distributions of some variables (eg, MVPA because of bounding at zero combined with low activity in that intensity), nonparametric Mann-Whitney U-tests examined between-group differences in group characteristics, gait, and physical activity variables.

All statistical analyses were performed in SPSS (IBM) with $\alpha = 0.05$. Post hoc adjustments for multiple comparisons were not performed (45), as all examined associations were biologically plausible, given that any difference in step count levels in this population could indicate differences in overall joint loading exposure.

RESULTS

The full sample (Table 1) consisted of 20 women and 37 men with KL grades of 2 or higher. The average daily wear time was 854 ± 79 minutes for the full sample and did not differ across step count quartiles ($P = 0.51$) or between TKA and no TKA groups ($P = 0.11$).

Significant positive correlations ($P < 0.05$) indicated that lower step count and lower MVPA were associated with less midstance

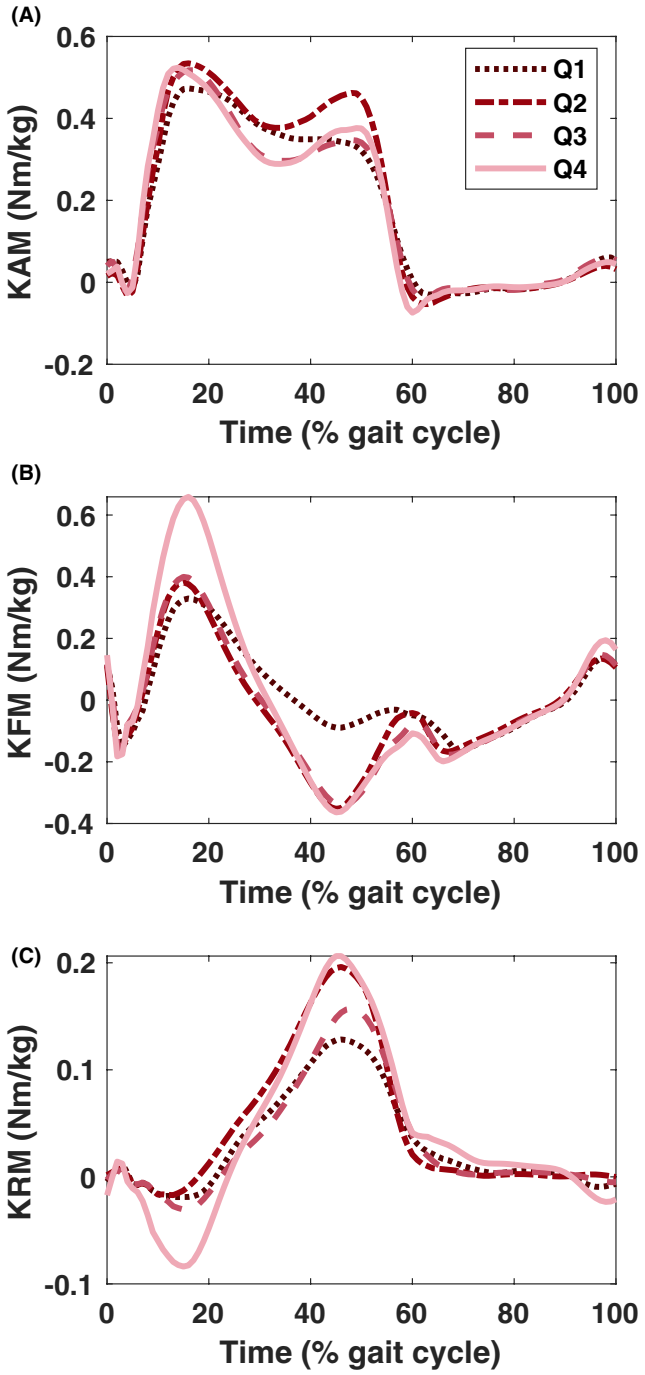

Figure 1. Moment waveforms across quartiles (Qs) of step count (Q1: 3915 ± 668 steps/day, n = 15; Q2: 5641 ± 641 steps/day, n = 14; Q3: 7646 ± 383, n = 14; Q4: 9784 ± 1316 steps/day, n = 14), normalized to body mass. **A**, Knee adduction moment (KAM). **B**, Knee flexion moment (KFM). **C**, Knee internal rotation moment (KRM). Abbreviation: **Q**, quartile.

KAM unloading (KAM PC2), lower overall KFM amplitude in early stance (KFM PC1), a smaller difference between early-stance KFM and late-stance extension moment (KFM PC2), and a smaller difference between external and internal knee rotation moment (KRM PC1) (Table 2). Significant negative correlations ($P < 0.05$) indicated that lower step count was associated with higher MH activity (PC1) and prolonged activity in midstance (PC2) for all three quadriceps and LH (Table 2). Similarly, significant negative correlations indicated lower MVPA was associated with higher MH activity (PC1) and prolonged midstance LH activity (PC2) (Table 2). There were no significant correlations between SED or LPA and any gait PC ($P > 0.05$ for all) (Table 2).

When the sample was divided into quartiles by step count, there were trends toward increasing LPA and MVPA and decreasing SED across step count quartiles, but the differences between consecutive quartiles were not all significant (Table 1). There were differences in radiographic severity, WOMAC pain, and knee extensor strength among quartiles and trends towards differences in sex ($P = 0.06$) and gait speed ($P = 0.07$) (Table 1). The two lowest quartiles had a smaller difference between early-stance and midstance KAM (KAM PC2; Figure 1A) and prolonged midstance RF activation (RF PC2; Figure 2C) when compared with the highest quartile (Table 3). Additionally, the lowest quartile had a smaller difference between early-stance flexion and late-stance extension moments (KFM PC2; Figure 1B) and prolonged midstance VM activation (VM PC2; Figure 2B) when compared with all other quartiles, a smaller external to internal rotation moment difference (KRM PC1; Figure 1C) when compared with the highest quartile, and prolonged midstance VL activation (VL PC2; Figure 2A) when compared with the two highest quartiles (Table 3). Prolonged midstance LH activation was found in the lowest quartile relative to the two highest quartiles and in the second lowest quartile relative to the highest quartile (LH PC2; Table 3; Figure 3A). Last, the highest quartile had a greater early-stance flexion moment magnitude (KFM PC1; Figure 1B) relative to all other quartiles (Table 3).

Individuals excluded from the longitudinal analysis represented a less severe group than those included, with lower radiographic scores, WOMAC scores, higher knee flexor strength, lower BMI, and higher gait speed (Table 4). At baseline, the TKA and no TKA groups were similar in terms of sex, age, mass, BMI, radiographic scores, and muscle strength, but the TKA group had higher WOMAC scores (Table 4) and baseline gait differences consistent with prior work (Supplementary Material). There were no differences in baseline physical activity metrics between groups (Table 5; Figure 4). The results of the sensitivity analysis including individuals with a KL grade of 2 were similar.

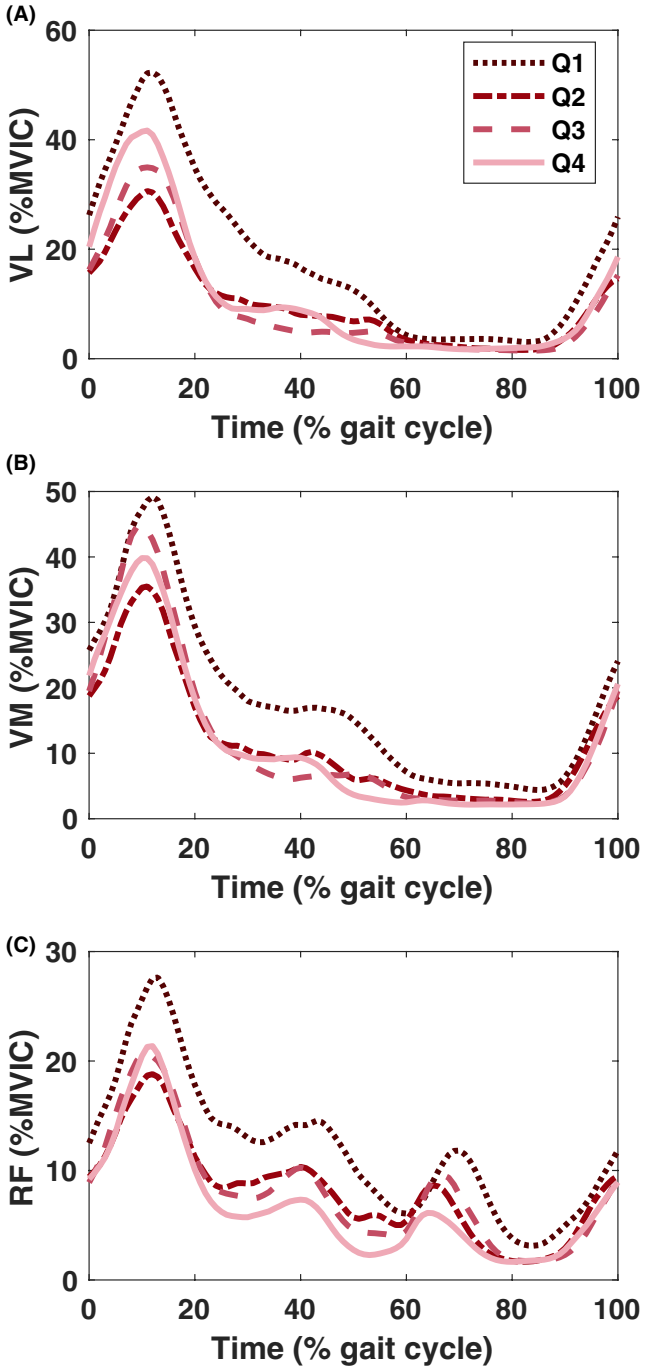

Figure 2. Quadriceps electromyography waveforms across quartiles (Qs) of step count (Q1: 3915 ± 668 steps/day, n = 15; Q2: 5641 ± 641 steps/day, n = 14; Q3: 7646 ± 383, n = 14; Q4: 9784 ± 1316 steps/day, n = 14], presented as percentage maximum voluntary isometric contraction (%MVIC). **A**, Vastus lateralis (VL). **B**, Vastus medialis (VM). **C**, Rectus femoris (RF).

DISCUSSION

Our primary hypothesis that step count, but not intensity-based metrics, would be related to gait patterns was partially supported, with significant correlations between gait patterns associated with clinical OA progression and both step count and MVPA. Further analyses examining trends across the quartiles of step count showed that these relationships were not consistent across the range of step counts seen in the current sample, with

Table 3. Gait data across quartiles of step count

PCs		Quartile 1 (n = 15)	Quartile 2 (n = 14)	Quartile 3 (n = 14)	Quartile 4 (n = 14)	*P* Value[a]	Pairwise Differences
Moment PCs, mean ± SD							
KAM	1	0.20 ± 0.91	0.73 ± 1.22	0.23 ± 1.12	0.29 ± 1.14	0.86	
	2	−0.19 ± 0.50	−0.30 ± 0.52	0.09 ± 0.62	0.09 ± 0.49	0.04*	1,2 v 4
KFM	1	−0.01 ± 0.79	−0.09 ± 1.63	0.07 ± 1.45	1.10 ± 1.45	0.04*	1,2,3 v 4
	2	−1.19 ± 1.00	0.07 ± 1.11	0.08 ± 0.96	0.22 ± 1.10	<0.01*	1 v 2,3,4
KRM	1	−0.13 ± 0.40	0.02 ± 0.39	−0.01 ± 0.39	0.29 ± 0.42	0.01*	1 v 4
	2	−0.16 ± 0.38	0.13 ± 0.35	−0.13 ± 0.29	−0.05 ± 0.33	0.84	
EMG PCs, mean ± SD[b]							
LG	1	244.1 ± 99.6	225.0 ± 82.5	235.9 ± 125.1	232.4 ± 86.0	0.93	
MG	1	212.3 ± 66.2	213.5 ± 142.5	211.1 ± 71.3	223.7 ± 84.8	0.65	
VL	1	232.9 ± 151.8	128.8 ± 45.7	137.0 ± 55.3	162.0 ± 100.6	0.14	
VM	1	216.6 ± 126.2	147.3 ± 60.3	166.6 ± 86.0	157.9 ± 83.4	0.27	
RF	1	131.4 ± 73.8	90.1 ± 34.4	92.9 ± 53.2	84.5 ± 53.1	0.07	
LH	1	180.6 ± 92.8	144.1 ± 80.8	158.4 ± 81.7	119.0 ± 62.5	0.10	
MH	1	171.8 ± 122.6	93.6 ± 27.1	116.2 ± 48.0	104.1 ± 71.5	0.14	
VL	2	9.8 ± 46.5	−1.8 ± 36.0	−22.7 ± 27.0	−28.2 ± 42.9	0.02*	1 v 3,4
VM	2	15.0 ± 38.8	−7.2 ± 41.3	−28.9 ± 31.4	−23.4 ± 27.6	0.01*	1 v 2,3,4
RF	2	32.6 ± 39.0	19.6 ± 25.8	13.2 ± 34.9	1.7 ± 21.9	0.01*	1,2 v 4
LH	2	21.0 ± 56.3	16.3 ± 60.7	−14.3 ± 44.2	−23.5 ± 23.3	<0.01*	1 v 3,4; 2 v 4
MH	2	−17.7 ± 65.9	−23.3 ± 28.6	−28.1 ± 21.4	−34.5 ± 24.5	0.05	

Abbreviation: EMG, electromyography; LG, lateral gastrocnemius; LH, lateral hamstring; LPA, light-intensity physical activity; KAM, knee adduction moment; KFM, knee flexion moment; KRM, knee rotation moment; MG, medial gastrocnemius; MH, medial hamstring; MVPA, moderate- to vigorous-intensity physical activity; PC, principal component; RF, rectus femoris; VL, vastus lateralis; VM, vastus medialis

Note, 1 = lowest to 4 = highest step count.

[a] Jonckheere-Terpstra test for ordered alternatives.

[b] EMG data were unavailable for n = 2 in Quartile 1, n = 2 in Quartile 3, and n = 1 in Quartile 4.

* Significant at $P < 0.05$.

few gait pattern differences seen among the higher step count quartiles. In our secondary analysis, individual baseline physical activity measures were not different between individuals who did or did not reach a TKA endpoint at a mean of 3.5-year follow-up. Collectively, these findings suggest that any potential added value that physical activity metrics may provide for understanding clinical OA progression is likely not an independent linear predictor of progression. Furthermore, the relationship between "at-risk" gait patterns and low physical activity levels could have implications on conservative management for individuals exhibiting these patterns.

Importantly, the current study identified that individuals with lower step counts had prolonged muscle activity and less dynamic loading patterns (smaller difference between early- and midstance/late-stance joint moments) compared with those with higher step counts. These differences could be related to severity (ie, greater KL grades in the lowest quartile and lower WOMAC pain scores in the highest quartile); however, the lower knee extensor strength observed in the lowest quartile combined with prolonged muscle activation could indicate greater potential for fatigue. These findings align with previous research that found a greater risk of incident functional limitation in individuals with knee OA who walk less than 6000 steps/day (46), as all the participants in the lowest quartile of the current study and half of those in the second lowest quartile were below this threshold. Patient symptoms, including functional disability, factor into TKA decisions (47), supporting the current finding of an association between low step count and gait patterns that are predictive of future clinical progression. It is not clear from the current data whether these less dynamic gait patterns lead to low levels of step count or vice versa; however, the lack of differences in gait patterns among the higher quartiles (with the exceptions of KFM PC1 and RF PC2) implies that joint loading frequency may contribute unique information to understanding OA progression only for those with a step count above a certain threshold. Thus, for those above a threshold of approximately 4000 to 6000 steps/day, joint loading frequency may provide additional information about progression risk beyond that provided by gait data. Further investigation is needed to explore the combined influence of gait and physical activity on clinical OA progression for those above this threshold.

Step count can be considered a surrogate metric of joint loading frequency and is easily understandable; however, exploring the relationships between gait and physical activity intensity could provide further insight into how joint loading accumulation in daily life is related to OA progression. With a few exceptions, similar correlations were found between MVPA and gait as those seen between step count and gait. The less dynamic joint moments and prolonged muscle activation associated with MVPA could indicate a higher risk of clinical progression (12) in individuals who do not engage in MVPA and should be explored further in longitudinal analyses. In contrast, SED and LPA were not correlated with any gait PCs. These results may indicate that MVPA

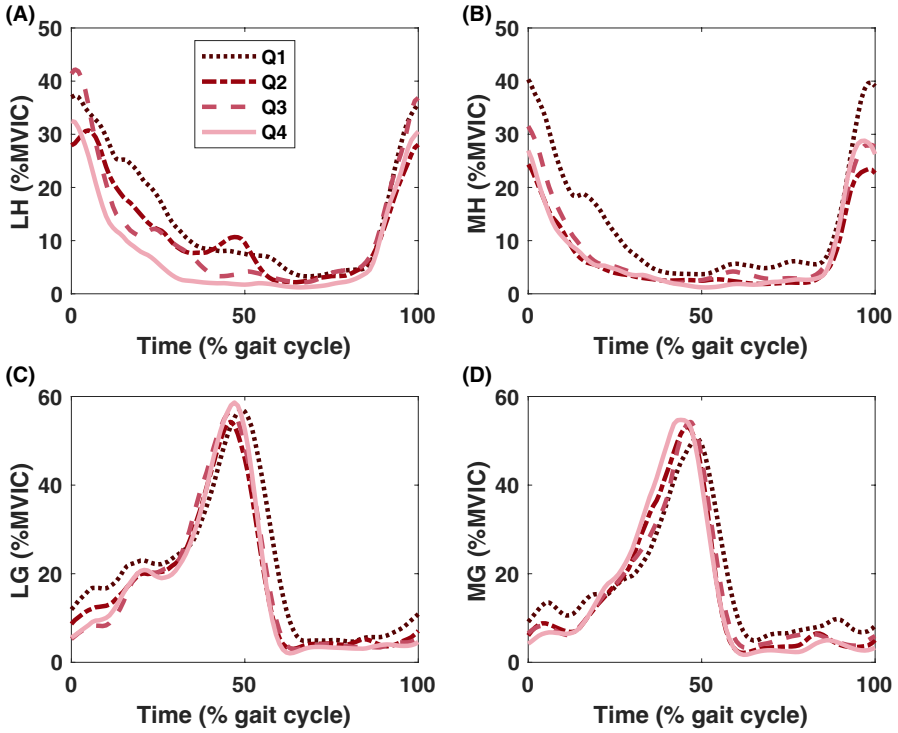

Figure 3. Hamstrings and gastrocnemius electromyography waveforms across quartiles (Qs) of step count [Q1: 3915 ± 668 steps/day, n = 15; Q2: 5641 ± 641 steps/day, n = 14; Q3: 7646 ± 383, n = 14; Q4: 9784 ± 1316 steps/day, n = 14], presented as percent maximum voluntary isometric contraction (%MVIC). **A**, Lateral hamstrings (LH). **B**, Medial hamstrings (MH). **C**, Lateral gastrocnemius (LG). **D**, Medial gastrocnemius (MG).

is more challenging or painful to perform for those who walk with less dynamic moments and prolonged muscle activation patterns and could be indicative of muscle fatigue and greater metabolic demand in those with these patterns. Prior work has shown higher LPA, regardless of MVPA, is inversely associated with incident disability (21), and it has been suggested that replacing SED with

Table 4. Sample characteristics for groups that did or did not reach the clinical TKA outcome at mean 3.5-year follow-up and those excluded from the analysis

	Excluded (n = 24)	Included (n = 33)	*P* Value[a]	TKA (n = 10)	No TKA (n = 23)	*P* Value[a]
Sex, female:male, n (% female)	6:18 (25)	14:19 (42)	0.17	4:6 (40)	10:13 (43)	0.85
Age, mean ± SD, y	61.9 ± 7.8	62.3 ± 6.3	0.46	61.7 ± 5.5	62.6 ± 6.6	0.71
Mass, mean ± SD, kg	86.5 ± 14.0	92.4 ± 18.9	0.19	86.9 ± 20.0	94.8 ± 18.3	0.31
BMI, mean ± SD, kg/m^2	29.3 ± 3.5	32.3 ± 6.3	0.08	31.9 ± 7.2	32.5 ± 6.0	0.77
Gait speed, mean ± SD, m/s	1.31 ± 0.20	1.22 ± 0.19	0.08	1.18 ± 0.21	1.24 ± 0.18	0.55
Radiographic scores[b]						
Kellgren-Lawrence grade (1, 2, 3, 4)	0, 10, 9, 2	0, 0, 19, 14	<0.01	0, 0, 4, 6	0, 0, 15, 8	0.27
Medial JSN (0, 1, 2, 3)	1, 10, 9, 1	0, 1, 19, 13	<0.01	0, 0, 4, 6	0, 1, 15, 7	0.17
Lateral JSN (0, 1, 2, 3)	12, 7, 1, 1	11, 15, 6, 1	0.09	5, 4, 1, 0	6, 11, 5, 1	0.18
Patellofemoral JSN (0, 1, 2, 3)	3, 13, 4, 1	1, 17, 12, 3	0.06	0, 4, 6, 0	1, 13, 6, 3	0.52
WOMAC, mean ± SD						
Pain (/20)	2.3 ± 2.9	4.8 ± 3.8	0.01	7.9 ± 3.0	3.5 ± 3.4	<0.01
Stiffness (/8)	1.0 ± 1.3	2.4 ± 1.5	<0.01	4.0 ± 0.7	1.7 ± 1.3	<0.01
Function (/68)	7.2 ± 6.4	15.9 ± 12.9	0.02	24.8 ± 13.0	12.1 ± 11.0	0.01
Strength, mean ± SDc						
Knee extensor, Nm/kg	1.36 ± 0.38	1.24 ± 0.36	0.23	1.22 ± 0.26	1.26 ± 0.40	0.89
Knee flexor, Nm/kg	0.78 ± 0.24	0.64 ± 0.19	0.03	0.65 ± 0.19	0.63 ± 0.19	0.37
Plantar flexor, Nm/kg	1.08 ± 0.38	0.88 ± 0.28	0.06	0.92 ± 0.32	0.86 ± 0.27	0.56
Time to follow-up, mean ± SD, y	-	-	-	3.5 ± 1.1	3.6 ± 0.9	0.92

Abbreviation: BMI, body mass index; JSN, joint space narrowing; TKA, total knee arthroplasty; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.
[a] From Mann-Whitney U-test except for sex (χ^2 test).
[b] Radiographic scores missing for n = 3 excluded individuals.
[c] Strength scores missing for n = 4 excluded individuals and n = 1 included individual in the no TKA group.

Table 5. Baseline physical activity differences between groups that did or did not reach the clinical TKA outcome at mean 3.5-year follow-up

	TKA (n = 10), Mean ± SD	No TKA (n = 23), Mean ± SD	Mean Difference (95% CI)	*P* Value[a]
Step count, steps/d	6551 ± 2573	6324 ± 2414	−227 (−2128 to 1675)	0.95
MVPA, % daily wear time	3.2 ± 2.2	2.5 ± 1.7	−0.6 (−2.0 to 0.8)	0.48
MVPA, min/d	26 ± 20	22 ± 15		
LPA, % daily wear time	34.2 ± 9.4	32.5 ± 10.5	−1.7 (−9.6 to 6.1)	0.60
LPA, min/d	279 ± 80	279 ± 90		
SED, % daily wear time	62.7 ± 9.5	65.0 ± 10.9	2.3 (−5.8 to 10.5)	0.50
SED, min/d	513 ± 92	563 ± 115		

Abbreviation: CI, confidence interval; LPA, light-intensity physical activity; MVPA, moderate- to vigorous-intensity physical activity; SED, sedentary behavior; TKA, total knee arthroplasty.
[a] Mann-Whitney U-test between TKA and no TKA groups.

LPA may be a suitable alternative for those who are not able to engage in MVPA (22). The lack of correlation between LPA or SED and gait PCs that have previously been associated with clinical progression indirectly supports this hypothesis of LPA as a suitable alternative and suggests that these intensity-based physical activity metrics provide information about loading exposure that is independent of gait mechanics. High SED, for example, could represent suboptimal levels of joint loading necessary for tissue health or muscle strength decline associated with atrophy.

In our subsample with longitudinal data, baseline accelerometer-derived metrics were not associated with knee OA clinical progression (TKA). The lack of association between physical activity metrics and clinical progression agrees with prior work showing that step count did not improve prediction of structural OA progression over a similar time frame (5). This result may indicate that this secondary analysis was underpowered, particularly given the large variability among individuals within each group (Figure 4); however, this may also indicate that joint loading frequency is less important to progression than joint loading magnitude over shorter time frames. As the current analysis shows joint loading frequency contributes unique information only above a certain threshold, the overall low step counts (~6000 steps/day) in both groups of this subsample may be another reason that there were no differences in joint loading frequency between those who progressed and those who did not. Joint loading frequency may be more relevant in an earlier OA cohort with higher physical activity levels. It should also be noted that the TKA group had higher WOMAC scores at baseline, and, although there were no statistically significant differences in radiographic scores, the median KL grade, and medial tibiofemoral joint space narrowing scores were higher in this group, suggesting severity differences at baseline could also have played a role in progression.

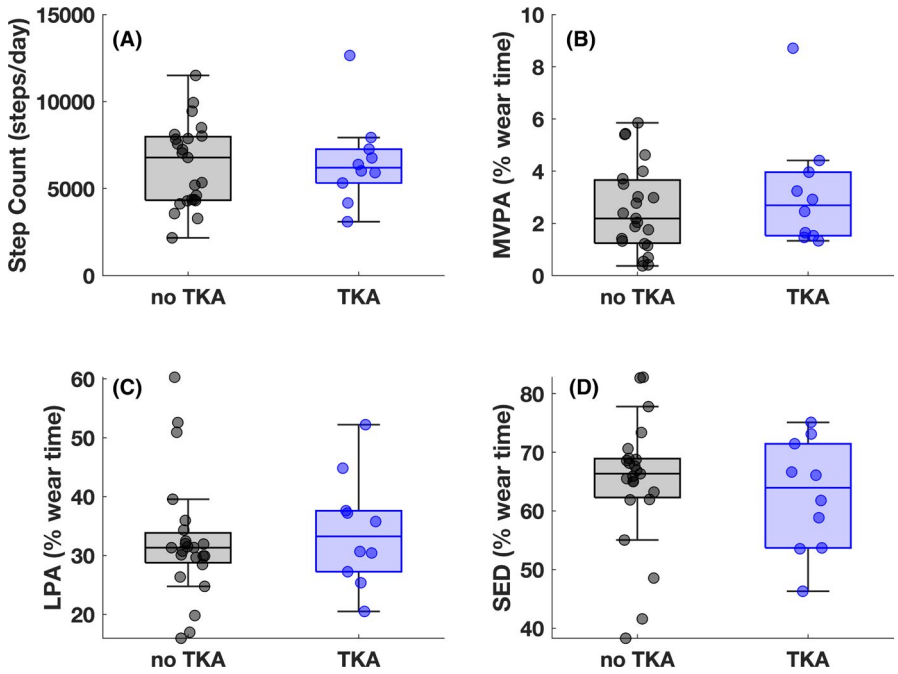

Figure 4. Baseline step count (**A**), moderate to vigorous physical activity (MVPA) (**B**), light physical activity (LPA) (**C**), and sedentary behavior (**D**) for groups that did (n = 10) or did not (n = 23) reach the clinical total knee arthroplasty (TKA) outcome at a mean follow-up of 3.5 years. Each circle represents data from an individual participant.

A limitation of the current study is that we did not have the sample size to create large multivariate models and therefore did not account for all potential confounders. In particular, both gait (48,49) and physical activity (50) differ by sex in those with knee OA, thus the relationship between joint loading magnitude and frequency, and its effects on OA outcomes, could differ by sex. Although there was a trend ($P = 0.06$) toward a higher proportion of women in the two lowest compared with the two highest step count quartiles, there was no significant difference in sex between TKA and no TKA groups in our secondary analysis. As sex and other confounders (eg, radiographic or pain severity) could affect both gait and physical activity, future work in larger samples should explore how these factors modify the relationships identified here. Furthermore, although our secondary analysis looked at baseline differences in physical activity between groups, given the complex relationships identified in the main analysis, future work examining how the interaction of gait and physical activity affects outcomes is warranted.

The results of the current study provide novel information on the complex relationships between joint loading magnitude, joint loading frequency, and clinical knee OA progression. Although joint loading metrics that have previously been associated with progression were correlated with step count and MVPA in our cross-sectional analysis, we were unable to show baseline differences in step count or MVPA between individuals who did or did not reach a TKA outcome at a mean follow-up of 3.5 years. Further research using cohorts at an earlier stage of OA that have higher overall activity levels may help identify potentially nonlinear interactions between gait and physical activity and their combined impact on clinical progression. It also remains to be seen whether increasing step count in individuals with lower overall activity could improve gait patterns or, alternatively, whether improving gait patterns would lead to increased step count in these individuals. Patient-specific interventions targeting gait, physical activity, or both may be needed for different individuals. In conclusion, these findings provide some of the first evidence of the complex relationships among gait, joint loading frequency, and OA progression, and suggest that joint loading frequency metrics derived from accelerometer data contribute unique information about the overall loading environment for individuals falling above a certain threshold.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Costello had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Costello, Astephen Wilson, Hubley-Kozey.
Acquisition of data. Costello.
Analysis and interpretation of data. Costello, Astephen Wilson, Hubley-Kozey.

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