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Strong independent associations between gait biomechanics and pain in patients with knee osteoarthritis

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ABSTRACT

We investigated the simple and multivariate associations between knee pain and gait biomechanics. 279 patients with medial knee osteoarthritis (OA) and discordant changes in pain between limbs after walking completed bilateral three-dimensional gait analysis. For each limb, patients rated their pain before and after a 6-min walk and the change in pain was recorded as an increase (≥ 1 points) or not (≤ 0 points). Among paired limbs, the simple and multivariate associations between an increase in pain and the external moments in each orthogonal plane were evaluated using conditional logistic regression. The analyses were then repeated for knee angles. Univariate analyses demonstrated associations in each plane that varied in both magnitude and direction, with larger associations for the knee moments [Odds Ratio (95% confidence interval) = first peak adduction moment: 2.80 (2.02, 3.88), second peak adduction moment: 2.36 (1.73, 3.24), adduction impulse: 6.65 (3.50, 12.62), flexion moment: 0.46 (0.36, 0.60), extension moment: 0.56 (0.44, 0.71), internal rotation moment: 7.54 (3.32, 17.13), external rotation moment: 0.001 (0.00, 0.04)]. Multivariate analyses with backward elimination resulted in a model including only the adduction impulse [5.35 (2.51, 11.42)], flexion moment [0.32 (0.22, 0.46)] and extension moment [0.28 (0.19, 0.42)]. The varus, flexion and extension angles were included in the final multivariate model for the knee angles. When between-person confounding is lessened by comparing limbs within patients, there are strong independent associations between knee pain and multiple external knee moments that vary in magnitude and direction. While controlling for other knee moments, a greater adduction impulse and lower flexion and extension moments were independently associated with greater odds of an increase in pain.

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1. Introduction

Altered biomechanics and pain are key features in knee osteoarthritis (OA), an extremely common disease that causes tremendous personal and societal burden (Felson, 2013; King et al., 2018). Symptomatic knee OA has been identified as the strongest contributor to walking difficulty (King et al., 2018); however, the associations between walking biomechanics and pain remain unclear. Measures derived from three-dimensional (3D) gait analysis are frequently used to quantify biomechanics in patients with OA. Knee angles and moments in each orthogonal plane can be determined throughout the stance phase of walking

and are associated with various aspects of disease (Andriacchi and Mundermann, 2006; Brouwer et al., 2007; Campbell et al., 2015; Hunter et al., 2008; Moyer et al., 2014).

Decreases in sagittal plane knee motion (e.g. knee flexion contractures) frequently occur in late stage knee OA (Campbell et al., 2015; Hunter et al., 2008), while more subtle changes in frontal and transverse plane knee motion observed earlier in disease may contribute to future structural degeneration (Andriacchi and Mundermann, 2006; Brouwer et al., 2007; Moyer et al., 2014). The external knee moments during stance are most commonly reported, as they are associated with different aspects of knee loading. Specifically, the knee adduction moment is widely accepted as a valid proxy for mediolateral distribution of load across the knee (Hurwitz et al., 1998; Kutzner et al., 2013) and a risk factor for structural disease progression in medial knee OA (Bennell et al., 2011; Miyazaki et al., 2002). Notably, changes in the knee adduction moment following intervention are related to clinically important

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changes (Birmingham et al., 2017; Prodromos et al., 1985). The knee flexion moment is also associated with medial contact force (Walter et al., 2010), may represent the net flexor-extensor muscle activity (Schipplein and Andriacchi, 1991) and provide an estimate of the overall magnitude of load across the knee. The knee flexion moment is also associated with structural OA progression (Chehab et al., 2014; Erhart-Hledik et al., 2015), decreases in magnitude over time (e.g. years) (Asay et al., 2018; Marriott et al., 2015) or may increase due to compensatory gait mechanisms (Jenkyn et al., 2008). Although less commonly reported, patients with greater OA severity may have greater internal rotation moments (Astephen et al., 2008) and lower external rotation moments (Landry et al., 2007). The peak internal rotation moment may also be associated with structural disease progression (Henriksen et al., 2012).

Pain is the most common complaint in individuals with knee OA and is commonly worsened by activities that load the knee and relieved by rest (Hunter et al., 2008). The associations between pain and gait biomechanics, however, are unclear. This is particularly true for the external knee moments, where previously reported associations are quite variable, often very low, and of questionable clinical importance (Astephen et al., 2016; Hall et al., 2017; Henriksen et al., 2012; Jones et al., 2014; Kim et al., 2004; Maly et al., 2008; O'Connell et al., 2016; Thorp et al., 2007; Zifchock et al., 2011). The majority of these studies have used cross-sectional designs that make comparisons between individuals (Astephen et al., 2016; Hall et al., 2017; Henriksen et al., 2012; Jones et al., 2014; Kim et al., 2004; Thorp et al., 2007) as well evaluating changes within individuals (Hurwitz et al., 2000), and may not account for multiple factors that influence an individual's perception of pain, such as previous pain encounters, expectations surrounding the effectiveness of analgesics, coping strategies and genetic predisposition (Colloca and Benedetti, 2006; Hunter et al., 2008; Mogil, 1999; Wager, 2005). As the interplay between extraneous factors and pain is exclusive to each individual, within-subject designs may be of benefit when studying these relationships. For example, the use of naturally matched pairs, where one limb within an individual is compared to the opposite limb, may help control for the influence of extraneous factors when studying knee OA pain (Birmingham et al., 2019; Neogi et al., 2009). This within-patient, between-knees design may provide an opportunity to more clearly determine the relationship between pain and load in patients with medial knee OA.

Additionally, while there may be value added by examining knee gait biomechanics in all three planes to represent different aspects of knee motion and loading, there may also be disadvantages related to redundancy of information, potential confounding and spurious results when testing multiple gait measures concurrently. In addition to the simple associations between pain and individual knee angles and moments in each plane, a better understanding of their multivariate relationships may provide greater insight into their individual contributions and perhaps their relative importance with respect to knee pain in response to loading. Therefore, the objectives of the present study were to investigate the simple and multivariate associations between pain and the knee angles and moments in each orthogonal plane during walking, while controlling for extraneous factors by comparing limbs within patients with medial knee OA. We hypothesized that the magnitude of knee angles and moments in each orthogonal plane during walking would be associated with an increase in knee pain.

2. Methods

2.1. Participants

Participants were from an ongoing registry of gait, imaging and patient-reported outcomes for patients with knee OA. Patients had

been referred to a tertiary care clinic and then subsequently to a biomechanics laboratory due to ongoing knee pain. All patients had a diagnosis of knee OA based on the criteria described by Altman and Gold (2007). All patients underwent a clinical examination by an orthopedic surgeon, during which patients were asked to show the location of greatest knee pain. For the present study, only patients with neutral or varus alignment (mechanical axis angle ≤ 0 degrees) and pain located primarily in the medial tibiofemoral compartment were included. All participants provided written informed consent, including the use of their data for future unknown research questions. The registry was approved by the institution's Research Ethics Board for Health Sciences Research Involving Human Subjects.

2.2. Pain assessment

We asked the participants to rate the level of pain in each knee using an 11-point numeric rating scale. The scale ranged from 0 to 10 with 0 representing no pain and 10 representing the worst pain possible. Patients rated pain in each knee immediately before and after completing a 6-minute walk. A stopwatch was used to record the time while the patient walked around an 80-foot track while wearing their own shoes. Patients were instructed to walk as far as possible without running and were informed that breaks were allowed if necessary (Butland et al., 1982; Finch et al., 2002). At approximately 5 min of walking, patients were informed they had almost completed the test. Otherwise, no further encouragement was provided.

2.3. Gait analysis

Patients completed bilateral gait analysis using an eight-camera motion capture system (Motion Analysis Corporation, Santa Rosa, CA) synchronized with a floor-mounted force platform (Advanced Mechanical Technology Inc., Watertown, MA). Passive-reflective markers were placed on bony landmarks using a 22-marker modified Helen Hayes marker set. During a static trial on the force platform, additional markers were placed over the medial knee joint line and medial malleolus to determine knee and ankle joint centers. Before gait testing, these four extra markers were removed. Marker (60 Hz) and forceplate (1200 Hz) data were collected while patients walked barefoot across a 10 m walkway at their typical walking speed. At least five trials for each extremity were collected. Inverse dynamics was used to calculate external knee moments from the camera and force plate data and were expressed relative to the tibial anatomical frame of reference (Leitch et al., 2013). The same methods and version of software were used to analyze gait data for all participants (Orthotrak 6.0, Motion Analysis Corporation) using methods previously reported to be reliable (Birmingham et al., 2007). Knee angles and moments were averaged over five trials and normalized to 100% stance. The greatest magnitudes for each knee angle and external moment in either a positive or negative direction were identified as the peaks for each gait cycle waveform. Moments were normalized to bodyweight and height ($BW \times Ht$). To simplify interpretation of the results, each knee angle and external moment was expressed as a positive value. We also calculated the knee adduction impulse ($BW \times Ht \times s$) by integrating the adduction component of the frontal plane knee moment waveform throughout stance (from heel strike to toe-off) with respect to time.

2.4. Statistical analysis

To enable conditional logistic regression, the change in pain for each knee was calculated by subtracting the pain rating completed before from the pain rating completed after the 6-minute walk.

Knees with an increase in pain (i.e. change score ≥ 1) were classified as “increased” whereas knees with either a decrease or no change in pain (i.e. change score ≤ 0) were classified as “not increased”. Participants with one knee classified as “increased” and the other “not increased” were identified as discordant pairs and included in the analysis. Participants with both knees classified the same (i.e. both “increased” knees or both “not increased” knees) were excluded from the analysis.

Knee angles and knee moments were evaluated in separate models. The knee angle variables evaluated were the peak varus, flexion, extension, internal rotation and external rotation angles. The external knee moment variables evaluated were the first peak adduction moment, second peak adduction moment, adduction impulse, peak flexion moment, peak extension moment, peak internal rotation moment and peak external rotation moment.

We first completed univariate conditional regression analyses to evaluate the independent association of each gait variable with change in knee pain after walking. We then completed a multivariate conditional logistic regression analysis including all knee angles or all knee moments, as independent variables. In this multivariate analysis, we entered each variable (except for the knee adduction impulse) into one block. A backwards elimination method was then performed to determine which of the independent variables were significant contributors to the overall model. For each step of the backwards elimination method, the variable with the lowest, non-significant odds ratio was removed until only measures of gait biomechanics with a statistically significant odds ratio remained. A second multivariate analysis was also completed for the external knee moments where we repeated the initial multivariate analysis after replacing the first and second peak knee adduction moments with the knee adduction impulse.

For every analysis, the independent variables were the gait variables and the dependent variable was the change in pain (either an increase or no change). Therefore, within patients, gait biomechanical variables were compared between knees discordant for changes in pain, producing an odds ratio (OR) that represented the odds of one limb experiencing an increase in pain compared to the opposite limb. We also examined the simple relationships among the knee angles or moments using Pearson correlation coefficients to help interpret the multivariate models. All gait variables were analyzed as continuous variables.

We completed additional analyses based on the results of the above analyses. We repeated our multivariate analyses after replacing the first and second peak knee adduction moments with the peak internal rotation moment (i.e. removing the peak adduction moments and adduction impulse from the overall model). Lastly, to help interpret the findings, the knee moments identified as significant contributors from our two primary multivariate analyses were also categorized into quartiles and the odds ratios calculated for each quartile.

3. Results

There were 608 patients (1216 knees) in the registry. Of these, 279 patients were identified as having discordant changes in pain after walking. Patient demographics and clinical characteristics for these 279 patients are presented in Table 1.

3.1. Pearson correlations

There was a moderate, statistically significant correlation between the flexion angle and extension angle ($r = -0.55$, $p < 0.001$) and a strong, statistically significant correlation between the internal rotation angle and the external rotation angle

Table 1

Patient demographics and clinical characteristics for the *increased pain* knees (cases) and *not increased pain* knees (controls) in patients with discordant changes in knee pain ($n = 279$ patients).

	Mean (SD)	
Sex, M/F	206/73	
Age, yr	47 (9.5)	
BMI, kg/m ²	29 (5.0)	
MAA, degrees		
Case Knees	-7.01 (4.5)	
Control Knees	-4.10 (3.7)	
	Number (%)	
Medial KL Grades	Case Knees	Control Knees
0	9 (3.2)	98 (35.1)
1	49 (17.6)	86 (30.8)
2	47 (16.8)	32 (11.5)
3	102 (36.6)	49 (17.6)
4	71 (25.4)	13 (4.7)

BMI, body mass index. MAA, mechanical axis angle. KL, Kellgren-Lawrence grades.

($r = -0.88$, $p < 0.001$). The full Pearson correlation coefficient matrix is presented in Table 2.

There was a strong, statistically significant correlation between the (i) first peak knee adduction moment and second peak knee adduction moment ($r = 0.79$, $p < 0.001$), adduction impulse ($r = 0.82$, $p < 0.001$) and internal rotation moment ($r = 0.72$, $p < 0.001$); (ii) second peak knee adduction moment and adduction impulse ($r = 0.87$, $p < 0.001$) and internal rotation moment ($r = 0.82$, $p < 0.001$); and (iii) adduction impulse and internal rotation moment ($r = 0.69$, $p < 0.001$).

3.2. Univariate analyses

There was a statistically significant, positive association between pain after walking and the peak knee varus angle (1.30 (1.22, 1.39), $p < 0.001$) and external rotation angle (1.03 (1.01, 1.05), $p < 0.015$). There was a statistically significant, negative association between pain after walking and the peak knee flexion angle (0.90 (0.86, 0.94), $p < 0.001$), extension angle (0.91 (0.87, 0.95), $p < 0.001$) and internal rotation angle (0.94 (0.92, 0.97), $p < 0.001$).

There was a statistically significant, positive association between pain after walking and the first peak knee adduction moment (OR (95%CI) = 2.80 (2.02, 3.88), $p < 0.001$), second peak knee adduction moment (2.36 (1.73, 3.24), $p < 0.001$), knee adduction impulse (6.65 (3.50, 12.62), $p < 0.001$) and peak knee internal rotation moment (7.54 (3.32, 17.13), $p < 0.001$). There was a statistically significant, negative association between pain after walking and the peak knee flexion moment (0.46 (0.36, 0.60), $p < 0.001$), peak knee extension moment (0.56 (0.44, 0.71), $p < 0.001$) and peak knee external rotation moment (0.001 (0.00, 0.04), $p < 0.001$).

3.3. Multivariate analyses

In the multivariate analysis for the knee angles, the final model included the peak knee varus angle (OR (95%CI) = 1.22 (1.14, 1.32), $p < 0.001$), flexion angle (0.83 (0.78, 0.89), $p < 0.001$) and extension angle (0.81 (0.76, 0.87), $p < 0.001$).

In the first multivariate analysis for the knee moments, the final model included the first peak knee adduction moment (OR (95%CI) = 2.62 (1.76, 3.90), $p < 0.001$), peak knee flexion moment (0.32 (0.22, 0.46), $p < 0.001$) and peak knee extension moment (0.28 (0.19, 0.42), $p < 0.001$). In the second multivariate analysis, the final model included the knee adduction impulse (5.35 (2.51, 11.42), $p < 0.001$), peak knee flexion moment (0.29 (0.20, 0.43),

Table 2
Pearson correlation coefficients among the peak knee angles (top) and the external knee moments (bottom) (n = 558 knees).

	Varus Angle	Flexion Angle	Extension Angle	IR Angle	ER Angle		
Varus Angle		-0.065	-0.008	-0.291 ^b	0.270 ^b		
Flexion Angle			-0.548 ^b	0.334 ^b	-0.192 ^b		
Extension Angle				-0.158 ^b	0.241 ^b		
IR Angle					-0.884 ^b		
ER Angle							
	1st Peak KAM	2nd Peak KAM	Adduction Impulse	Flexion Moment	Extension Moment	IR Moment	ER Moment
1st Peak KAM		0.793 ^b	0.820 ^b	0.036	0.249 ^b	0.716 ^b	0.045
2nd Peak KAM			0.871 ^b	0.080	0.182 ^b	0.820 ^b	0.058
Adduction Impulse				-0.064	0.093 ^a	0.694 ^b	0.034
Flexion Moment					-0.163 ^b	0.119 ^b	0.282 ^b
Extension Moment						0.285 ^b	0.188 ^b
IR Moment							0.061
ER Moment							

KAM, knee adduction moment. IR, knee internal rotation. ER, knee external rotation.

^a Correlation is significant at the 0.05 level.

^b Correlation is significant at the 0.01 level.

$p < 0.001$) and peak knee extension moment (0.29 (0.20, 0.42), $p < 0.001$).

3.4. Additional analyses

Given the high correlation between the frontal plane knee moment variables and peak internal rotation moment, we repeated our original multivariate analyses after removing the knee adduction moment (peaks and impulse) to identify the independent effects of the peak internal rotation moment. For both multivariate analyses, the final model included the peak knee flexion, extension and internal rotation moments.

As the multivariate analyses identified the first peak knee adduction moment (or adduction impulse), peak flexion moment and peak extension moment as significant contributors to the final models, we also completed univariate conditional logistic regression analyses after categorizing each of these knee moments into quartiles. Fig. 1 shows the significant dose-response association between these measures of knee load and increased knee pain. For the first peak adduction moment and adduction impulse models, higher quartiles (i.e. greater external knee moments) were associated with greater odds of increased pain (Fig. 1). For the peak flexion and extension moment models, higher quartiles were associated with lower odds of increased pain (i.e. stronger odd ratios, Fig. 1).

We also investigated the effect of using different cut-off values for categorizing “increased pain” knees versus “no increased pain” knees. Results were consistent with our original analyses. The univariate analyses were also repeated after stratifying by sex. Results for both males and females were consistent with our original analyses.

4. Discussion

The present study investigated the simple and multivariate associations between pain and commonly reported gait biomechanics in the frontal, sagittal and transverse planes during walking, while controlling for extraneous factors by comparing limbs within patients. The univariate conditional regression analyses illustrate several strong associations between the external knee moments, in all three planes of motion, and an increase in knee pain after 6 min of walking. These associations varied in both magnitude and direction. For the first and second peak knee adduction moments, adduction impulse and internal rotation moment, greater values were associated with greater odds of experiencing an increase in pain after walking, ranging from an OR of about 2

(i.e. second peak knee adduction moment) to 7 (i.e. peak internal rotation moment). In contrast, greater knee flexion, extension and external rotation moments were associated with decreased odds of an increase in pain. For the peak knee angles, significant associations were also obtained from the univariate conditional regression analyses; however, these associations were quite low, indicating a weaker relationship with pain compared to the external knee moments.

Importantly, the results of the multivariate analyses indicated that the first peak knee adduction moment (or adduction impulse), flexion and extension moments were all significant contributors to the final model. Thus, knee moments in the frontal and sagittal planes were independently associated with increased pain, with quite different implications. Specifically, while controlling for the other knee moments, for every one unit increase in the knee adduction moment, there was 2.6 times the odds of increased pain compared to the opposite knee. Alternatively, while controlling for the other knee moments, for every one unit increase in the peak flexion moment, there was 0.32 times the odds of increased pain compared to the opposite knee. This independent association between the peak adduction and flexion moments has been previously observed (Jones et al., 2014). Additionally, splitting the sample into quartiles helped describe the implications of walking with a (i) larger first peak knee adduction moment and adduction impulse, and (ii) reduced peak knee flexion and extension moments. For example, knees in the highest adduction moment quartile (i.e. quartile 4) had approximately 10 times greater odds of experiencing pain compared to knees in the lowest adduction moment quartile (i.e. quartile 1) (Fig. 1). Alternatively, knees in the highest flexion moment quartile (i.e. quartile 4) had approximately 0.1 times greater odds of experiencing pain compared to knees in the lowest flexion quartile (i.e. quartile 1) (Fig. 1).

The associations between pain and the frontal plane knee moments are consistent with previous studies showing the adduction moment can distinguish well between radiographic disease severities (Kean et al., 2012), is associated with measures of medial compartment OA progression (Bennell et al., 2011; Miyazaki et al., 2002; Erhart-Hledik et al., 2015; Chang et al., 2015) and changes in the adduction moment are related to clinically important changes (Birmingham et al., 2017; Prodromos et al., 1985). The association between the peak internal rotation moment and pain is also consistent with previous results suggesting a greater internal rotation moment is associated with greater disease severity (Aststephen et al., 2008).

The significant Pearson correlations between the internal rotation moment and frontal plane moments, as well as elimination

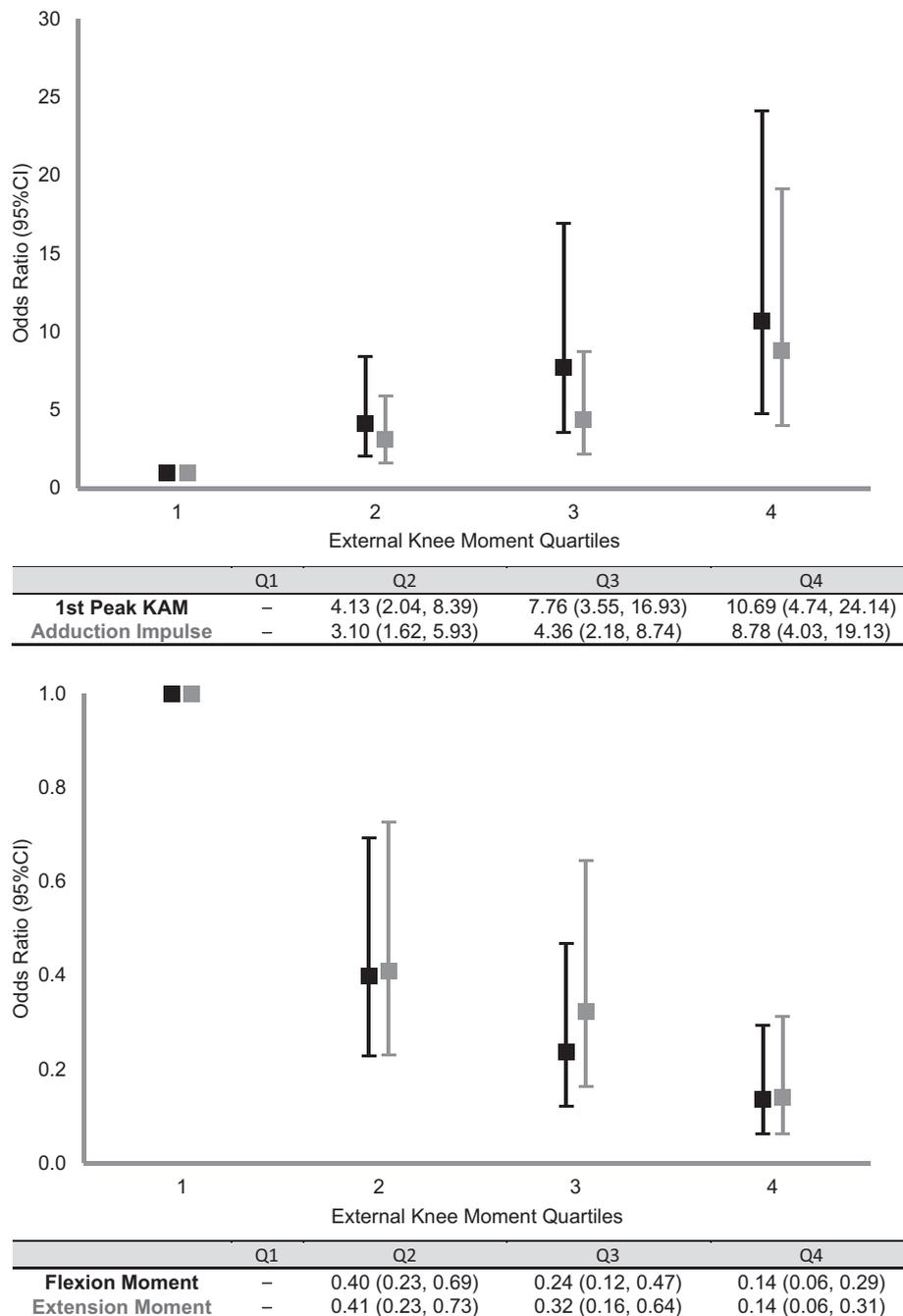


Fig. 1. Odds ratios and 95% confidence intervals (CI) from conditional logistic regression describing the association between increased knee pain and quartiles (Q) of knee load for the first peak knee adduction moment (KAM) (top black), knee adduction impulse (top grey), peak knee flexion moment (bottom black) and peak knee extension moment (bottom grey) ($n = 558$ knees). Quartile 1 is the reference. The y-axis is in logarithmic scale.

of the internal rotation moment from the multivariate models, suggests these knee moments are either describing similar gait metrics and/or are a function of how each moment is calculated (Piazza and Cavanaugh, 2000; Blankevoort et al., 1988; Kadaba et al., 1990). A high association between the peak adduction moment and internal rotation moment ($r = 0.82$) has been previously observed in individuals with varus alignment (Stief et al., 2014).

The relationship between pain and the peak knee flexion and extension moments were negative, so that greater flexion and extension moments were associated with lower odds of experiencing an increase in pain after walking. This negative association would suggest that higher sagittal plane knee moments may have a protective effect against pain and the disease mechanisms that

elicit pain. Conversely, this negative association would also suggest that individuals with lower peak flexion and extension moments may be more susceptible to developing knee pain. A gradual reduction in the knee flexion moment over time has been observed in patients with medial knee OA (Asay et al., 2018) and their contralateral limbs (Marriott et al., 2015).

Although the present moderate-to-strong associations between knee pain and external knee moments may seem to contrast previous studies evaluating this relationship, differences in study designs must be emphasized (Maly et al., 2008; Jones et al., 2014; O'Connell et al., 2016; Zifchock et al., 2011). Most importantly, our study used a within-subjects design which mitigated the influence of factors that affect knee pain perception, such as pain medication (Hunter et al., 2008; Colloca and Benedetti,

2006; Mogil, 1999; Wager, 2005). Notably, the within-patient design also controls for biomechanical variables such as walking speed and footwear.

In contrast to other studies that evaluated the relationship between biomechanics and symptoms in patients with knee OA, the main strength of our study was the ability to reduce the influence of extraneous factors by comparing limbs within individuals. Also, our sample size of 279 patients was larger than samples from similar cross-sectional studies (Henriksen et al., 2012; Hall et al., 2017; Kim et al., 2004; Maly et al., 2008; Jones et al., 2014; Thorp et al., 2007; Hurwitz et al., 2000; Birmingham et al., 2019), suggesting greater precision. Limitations of our study also need to be acknowledged. The present results should only be generalized to male patients with medial knee OA and the relationship between pain and load may differ for female individuals with lateral tibiofemoral OA and patellofemoral OA (Leitch et al., 2013). Additionally, future models that combine different aspects of gait data (such as modeled loads, the total joint moment, the difference between peak moments, gait speed, etc.) may demonstrate different (greater or lesser) associations with pain than the present statistical models. Our criteria used to define knee pain categories were selected somewhat arbitrarily based on a cut-off value of 1 point. The conditional logistic analysis also required discordant pairs of knee pain and therefore, participants with both knees classified the same were excluded. The ability to accurately and reliably measure transverse plane biomechanics is less compared to the frontal and sagittal planes (Krauss et al., 2012; Lobet et al., 2010). Therefore, results for the internal rotation moment should be interpreted cautiously. Future studies should examine the relationship between knee pain and knee biomechanics in the context of different pain models, such as different methods of pain modulation, pain in the context of knee instability and varying degrees of pain chronicity, that may help to clarify why some patients, although few, experience a decrease in pain after walking. These models should also investigate this relationship in the context of more strenuous activities, such as climbing stairs, and in the presence of gait compensations, such as toe-out angle or lateral trunk lean, as these activities and gait patterns may elicit different associations of gait biomechanics with pain.

In conclusion, results of our study illustrate that the external knee moments in all three planes of motion, and the adduction impulse, are associated with an increase in pain when the influence of extraneous factors is reduced by comparing, within individuals, limbs discordant in pain. These associations vary in both magnitude and direction. While controlling for other knee moments, a greater peak adduction moment (or adduction impulse) and lower flexion and extension moments were independently associated with greater odds of an increase in pain.

Author Contributions

KM and TB: Study conception and design, data acquisition, analysis and interpretation (1); drafting the manuscript and revising the manuscript for intellectual content (2); and approval of the final submission (3). KL and RP: Data acquisition (1); manuscript drafting (2); and approval of the final submission (3). JRG: Study conception and design and data acquisition (1); manuscript drafting (2); and approval of the final submission (3). Each of the authors has read and concurs with the content in the manuscript.

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Declaration of Competing Interest

There are no conflicts of interest to disclose.

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