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Relationship between knee joint contact forces and external knee joint moments in patients with medial knee osteoarthritis: effects of gait modifications

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SUMMARY

Objective: To evaluate 1) the relationship between the knee contact force (KCF) and knee adduction and flexion moments (KAM and KFM) during normal gait in people with medial knee osteoarthritis (KOA), 2) the effects on the KCF of walking with a modified gait pattern and 3) the relationship between changes in the KCF and changes in the knee moments.
Method: We modeled the gait biomechanics of thirty-five patients with medial KOA using the AnyBody Modeling System during normal gait and two modified gait patterns. We calculated the internal KCF and evaluated the external joint moments (KAM and KFM) against it using linear regression analyses.
Results: First peak medial KCF was associated with first peak KAM ($R^2 = 0.60$) and with KAM and KFM ($R^2 = 0.73$). Walking with both modified gait patterns reduced KAM ($P = 0.002$) and the medial to total KCF ratio ($P < 0.001$) at the first peak. Changes in KAM during modified gait were moderately associated with changes in the medial KCF at the first peak ($R^2 = 0.54$ and 0.53).
Conclusions: At the first peak, KAM is a reasonable substitute for the medial contact force, but not at the second peak. First peak KFM is also a significant contributor to the medial KCF. At the first peak, walking with a modified gait reduced the ratio of the medial to total KCF but not the medial KCF itself. To determine the effects of gait modifications on cartilage loading and disease progression, longitudinal studies and individualized modeling, accounting for motion control, would be required.

Introduction

Increased dynamic knee loading is associated with progression of medial knee osteoarthritis (KOA)[1,2]. The knee adduction moment (KAM) is often reported in studies investigating knee biomechanics[3,4]. Higher KAM is associated with radiographic changes in the knee joint structure and cartilage degeneration[2,5]. KAM is considered to be a surrogate measure for knee contact force (KCF) which is assumed to represent the detrimental biomechanics leading to cartilage changes. However since KAM is only a first approximation of KCF[6], it has been suggested that the knee flexion moment (KFM) should be taken into account as well[5,7,8]. In studies measuring KCF using instrumented prostheses, the association between KAM and KCF ranges from $R^2 = 0.09$ to $R^2 = 0.97$[6]. Unfortunately, results are typically based on low-powered studies and direct measurement of KCF is not possible in the intact knee. Furthermore, muscle activation patterns after knee arthroplasty (TKA) may not be representative of activation patterns in healthy or KOA patients[9]. As such, relationships between KAM and KCF in TKA subjects may not be generalizable to the healthy or KOA population.

Estimation of KCF is possible through computational musculoskeletal modeling systems, such as the AnyBody Modeling System

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(AMS, AnyBody Technology, Aalborg, Denmark) or OpenSim[10,11]. Studies based on musculoskeletal modeling investigating associations between KAM and KCF have reported R^2 values from 0.36 (in young healthy subjects)[12], 0.52 (in older adults)[13] to 0.6 (in young subjects post-ACL reconstruction)[8]. These values suggest only moderate association between the measured KAM and estimated KCF.

Despite the influence of biomechanical factors in KOA, to date modeling studies have largely focused on healthy individuals[14], individuals post-ACL reconstruction[8] or individuals post-TKA[15,16]. Few studies have reported the KCF in KOA patients and fewer still have reported changes in KCF in KOA patients following intervention, with assessment of the biomechanical effects usually limited to changes in KAM and KFM.

With increasing KOA incidence and an increasing need to address the underlying biomechanical factors, there is now considerable research focus on understanding the effectiveness of gait modifications as a conservative intervention for reducing KAM[17,18]. Gait modifications such as modifying the foot progression angle (FPA) can successfully reduce KAM and have also resulted in improvements in pain and function[19,20]. However, a reduction in KAM does not always lead to a reduction in KCF: changes in medial KCF (mKCF) in subjects with instrumented prostheses ranged from 18% increase[21] through 4.5%[22] to 18%[23] to 45% decrease[24] depending on the type of gait modification and the phase of the gait cycle. However, as argued previously, these results may not be generalizable to the KOA population.

Our first aim was to investigate the relationship between the external knee moments (i.e., KAM and KFM) and the modeled KCF during steady-state walking in patients with medial KOA. We hypothesized that KAM would be associated with mKCF and total KCF (tKCF) at the first peak but not at the second[6]. Our second aim was to investigate changes in the mKCF and tKCF following toe-in and step width gait modification. We hypothesized that walking with either toe-in gait or with wider steps would reduce the first peak of the mKCF, in line with reductions in KAM[25]. Finally, our third aim was to investigate how *changes* in external knee moments were associated with *changes* in the mKCF. We hypothesized that KAM changes would be strongly associated with mKCF changes, similar to the relationship between these parameters reported pre- and post-high tibial osteotomy[26].

Method

Participants

This study uses data collected for a previous study[27] with forty participants with medial KOA. Data from 35 of 40 participants were analyzed; demographics are presented in Table I. Five participants were excluded due to incorrect format of the input data for the model. Characteristics of the included participants ($n = 35$) were not significantly different to the excluded participants ($n = 5$). Ethical approval was granted by the VUmc Medical Ethics committee and all participants provided written consent. Inclusion and exclusion criteria for the study are described in Richards *et al.*[27].

Table I
Demographics of participants included in the study ($n = 35$)

Characteristic	Mean (SD)	Range
Age (yr)	62.3 (5.91)	51.0–71.7
Height (m)	1.73 (0.09)	1.53–1.92
Mass (kg)	76.06 (10.35)	57.2–98.40
BMI (kg/m^2)	25.48 (2.63)	20.03–33.69
Gender	M 13 F 22 (63%)	
Kellgren and Lawrence Grade (of the more affected knee)	I: 16, II: 7, III: 8, IV: 4.	

Gait analysis

Participants attended the Virtual Reality laboratory at the VUmc for 3D instrumented treadmill-based gait analysis[27]. In this secondary analysis, we used three gait conditions from our previous study; 1) normal gait, 2) toe-in gait and 3) wide-steps gait. For each modification, participants received real-time feedback based on a pre-defined target for the modification[27].

Musculoskeletal modeling and data analysis

The .c3d files from the raw data collection were used as input for a lower limb musculoskeletal model run in AnyBody Modeling System[28]. Validation of a similar model against data from an instrumented knee showed strong agreement with the experimental data[28]. Recently, small modifications have been made to the model to improve the predictions of the second peak. Results of validation of the current model are presented in Appendix A. Model anatomy was defined based on cadaveric measurements from the Twente Lower Extremity (TLEM) dataset[29]. Initially, a stick figure was created based on the experimental data for the static trial and morphed with the musculoskeletal template geometry to create a scaled musculoskeletal model[28]. Inverse kinematics were used to calculate the joint angles based on the motion capture data. During this step, the knee was modeled as ball-and-socket joint. These angles and the morphed model and ground reaction forces provided input to an inverse dynamics analysis to calculate joint moments, muscle forces and KCF. Dynamic equilibrium equations were solved using muscle activities squared as the muscle recruitment (optimization criteria). Non-negativity constraints were applied to ensure that muscles only pull and not push[11]. To account for resistance against varus–valgus and internal–external provided by the ligamentous structures of the knee, reaction moments in these directions were included in the inverse dynamics, allowing the muscles crossing the knee to only balance the flexion–extension moment. Joint moments and forces were calculated based on the International Society of Biomechanics (ISB) segment definitions[30] and the Grood and Suntay method was used to express the knee kinematics and kinetics[31]. Joint contact forces (compressive forces only) were calculated as the net loading on the joint resulting from muscular forces, gravitational forces, inertial forces and ground reaction forces and moments. Joint moments and forces were expressed in the shank coordinate system[31] and normalized to body weight and the product of body weight and height, respectively. The medial-lateral distribution of the KCF was calculated by applying a moment equilibrium (equation (1)) and force equilibrium (equation (2)) in the frontal plane. The moment arms for the condyles were estimated based on reported ratios of the condylar width relative to the knee width from X-Rays of the knees of 101 subjects[32]. Validation of the force and moment equilibriums are presented in Appendix A.

$$KAM + KCF_{lateral} \cdot CMA_L - KCF_{medial} \cdot CMA_M = 0 \quad (1)$$

where $KCF_{lateral}$ is the contact force in the lateral knee compartment.

KCF_{medial} is the contact force in the knee in medial knee compartment.

CMA_L is the length of the lateral condyle moment arm.

KAM is the KAM in the shank coordinate system and

CMA_M is the length of the medial condyle moment arm.

$$KCF_{total} = KCF_{lateral} + KCF_{medial} \quad (2)$$

where KCF_{total} is the total contact force.

Data analysis and extraction

Data were time-normalized to 100% gait cycle using the ground reaction force data with a threshold of 25 N to determine gait events. From each complete gait cycle we extracted peak values for the mKCF and tKCF during the first (1–50%) and second (51–100%) half of the stance phase. Using these timings, we identified peak values in the external KAM and KFM (flexor and extensor). Thus, for each gait trial, we extracted multiple values for KAM and KFM (i.e., from several strides, mean 22 ± 8), where each value corresponded to a peak in the medial or total contact force. For the flexion moment, we also extracted the absolute peak value over the full gait cycle. Finally, KAM impulse, the magnitude of KFM impulse and the mKCF and tKCF impulse were calculated per cycle.

Statistical analysis

Prior to statistical analysis, outcome measures were checked for normality with Shapiro–Wilk and Kolmogorov–Smirnov tests. Where deviations from normal distribution were found, non-parametric tests were used.

To investigate our first aim we used linear regression analyses with either the first, second or both peaks of the mKCF or tKCF as the dependent variable. Independent variables were peak KAM (first, second or both peaks) and peak KFM (first, second or both peaks). When both peaks were used in the regression analysis, correlation was with both first and second peak of the KCF. For the peak KFM, we considered the magnitude of KFM since both KFM and knee extension moments may be associated with the KCF. Furthermore, we evaluated the relationship between the ratio of the mKCF to tKCF (at the peak values) and KAM (first, second or both peaks) and KFM (first, second or both peaks) since KAM may better represent the distribution of the KCF than the mKCF itself[33,34]. Furthermore, we modeled the relationship between KAM impulse, magnitude of the KFM impulse, the mKCF and tKCF impulse and the ratio of the mKCF to tKCF. For all regression analyses, data were checked for significant outliers using case wise diagnostics within SPSS. Data were also checked for independence of observations, using the Durbin–Watson statistic in SPSS. Homoscedasticity and normality of the residuals were checked visually using histograms, scatter plots and normal P–P plots. Assumptions were fulfilled. The analysis unit was the number of patients ($n = 35$) and all data were from normal walking condition (i.e., walking without gait modifications).

Second, we investigated the effect of the gait modifications on the external joint moments and internal KCF. For this analysis, the analysis unit was the number of patients ($n = 35$) with three conditions (normal gait, toe-in gait and wide-steps gait). Therefore, we used repeated measures analysis of variance (ANOVA) and the Friedman test in the case of deviations from normal distribution, with the type of gait pattern as the independent variable and the peak internal KCF (medial or total), peak external force (KAM or KFM), KAM impulse, KCF impulse (medial or total) or mKCF to tKCF ratio as the dependent variable. We used post-hoc pairwise comparisons with Sidak correction to determine which gait modifications differed from normal gait. For non-parametric data, we used the Wilcoxon signed rank test for pairwise comparisons.

Finally, we evaluated the association between *changes* in the external joint moments and *changes* in the mKCF. For this regression model, we considered changes in the first and second peak mKCF as the dependent variable and *change* in the peak KAM (first, second) and *change* in peak KFM (first, second) as independent variables. Statistical significance was set to $\alpha = 0.05$. All analyses were performed using SPSS software, version 22.0 (SPSS, Chicago, IL, USA).

Results

At the first peak, we found a moderate to strong statistical association between KAM, KFM and mKCF, (adjusted $R^2 = 0.60$ [95% CI 0.47 to 0.68] for the KAM only model and 0.73 [0.63, 0.80] for KAM and KFM together); Table II and Fig. 1. Statistical association between the external moments and mKCF at the second peak was lower (adjusted $R^2 = 0.44$ [0.29, 0.55] and 0.43 [0.26, 0.54] respectively). Statistical associations between KAM and tKCF were generally weak or moderate (maximum adjusted $R^2 = 0.44$ [0.27, 0.54]) and KFM did not contribute significantly ($P > 0.05$). Including both first and second peak KAM in the models reduced the association of the external loads with the internal knee joint forces and increased the root-mean-square (RMS) error.

Peak KAM was statistically associated with the mKCF to tKCF ratio, particularly at the second peak, adjusted $R^2 = 0.86$ [0.80, 0.89] (Table II). Peak KFM was also a significant predictor at the first peak ($P < 0.001$), but not at the second ($P = 0.211$).

We observed a strong and significant statistical association between KAM impulse and the ratio of the medial to tKCF impulse (adjusted $R^2 = 0.83$ [0.76, 0.87]) with an error of less than 4%. KFM impulse did not significantly contribute to the mKCF to tKCF impulse ratio.

First peak KAM was statistically reduced while walking with toe-in gait and wide-steps gait (mean reduction of 0.16% BW*Ht, $P = 0.002$), Table III. Unlike KAM, where the first peak was higher than the second, mKCF and tKCF were higher at the second peak compared to the first in all conditions. First peak mKCF was significantly different between the three modified walking conditions ($P = 0.019$), Fig. S2 (Appendix B). However, post-hoc testing did not reveal significant differences compared to normal walking ($P = 0.986$ and $P = 0.064$ respectively). First peak tKCF was significantly different between toe-in gait and wide-steps gait ($P = 0.047$), but again no significant differences were found relative to normal walking ($P = 0.088$ and $P = 1.000$). Second peak mKCF and second peak tKCF were both significantly reduced during toe-in gait (mean difference 0.07BW, $P = 0.002$ and 0.15BW, $P < 0.001$, respectively). KAM, mKCF and tKCF impulse were unchanged during modified gait walking ($P > 0.05$). The ratio of the mKCF to tKCF ratio decreased at the first peak compared with normal gait condition in both modified gait conditions (mean reduction of 0.02, $P < 0.001$); Table III. At the second peak, the ratio increased during the toe-in gait (mean increase of 0.01, $P = 0.020$) but not during wide-steps gait.

A moderate statistical association between change in (Δ) first peak mKCF and Δ first peak KAM was found (adjusted $R^2 = 0.54$ [95% CI 0.38, 0.64]), Table IV, during walking with toe-in gait with respect to normal walking. Adding Δ first peak KFM to the model improved the fit to $R^2 = 0.74$ [0.63, 0.80], and reduced the RMS error. The unstandardized beta for ΔKAM (0.27 [0.17, 0.34]) was more than twice that for ΔKFM (0.11 [0.08, 0.16]). The model for the wide-steps condition (Table IV) showed similar results, although the contribution of Δ first peak KAM was lower than for the toe-in model. A weak statistical association was found between Δ second peak KAM and Δ second peak KFM and Δ second peak mKCF (adjusted $R^2 < 0.28$).

A weak statistical association was found between Δ first peak KAM and Δ ratio of peak mKCF to tKCF (adjusted $R^2 = 0.32$ [0.15, 0.45] for toe-in gait and 0.29 [0.12, 0.43] for wide-steps gait). Including Δ peak KFM improved the models to adjusted $R^2 = 0.55$ [0.38, 0.64] and 0.62 [0.46, 0.70] respectively. At the second peak, the statistical association between Δ peak KAM and ΔmKCF was stronger (Table IV) ($R^2 > 0.71$).

Table II
Regression equations with corresponding R^2 and RMS errors for fitting contact forces as a function of the external loads during normal walking

Part of gait cycle	Contact force	Regression equation	c1 [95% CI]	c2 [95% CI]	c3 [95% CI]	Adj. R^2 [95% CI]	RMS error (BW)	Percentage error
First peak stance phase	First peak medial	c1 + c2 KAM	1.000 [0.846, 1.205]	0.283 [0.227, 0.327]		0.597 [0.465, 0.680]	0.223	11.66
		c1 + c2 KAM + c3 |KFM|	0.829 [0.671, 1.019]	0.239 [0.177, 0.282]	0.102 [0.064, 0.145]	0.733 [0.630, 0.796]	0.181	9.75
	First peak total	c1 + c2 KAM	1.925 [1.638, 2.241]	0.131 [0.043, 0.214]		0.098 [0.005, 0.222]	0.362	15.50
		c1 + c2 KAM + c3|KFM|	1.626 [1.326, 1.927]	0.054 **[−0.033, 0.134]**	0.177 [0.122, 0.246]	0.441 [0.274, 0.544]	0.285	12.23
	Medial to total force ratio (at first peak)	c1 + c2 KAM	0.573 [0.522, 0.614]	0.077 [0.066, 0.095]		0.592 [0.460, 0.676]	0.061	7.43
		c1 + c2 KAM + c3 |KFM|	0.609 [0.556, 0.614]	0.087 [0.073, 0.105]	−0.022 [−0.034, −0.010]	0.672 [0.551, 0.737]	0.055	6.69
Second peak stance phase	Second peak medial	c1 + c2 KAM	1.531 [1.332, 1.758]	0.277 [0.186, 0.363]		0.439 [0.286, 0.549]	0.281	13.13
		c1 + c2 KAM + c3|KFM|	1.531 [1.322, 1.774]	0.277 [0.186, 0.363]	**0.000 [−0.100, 0.083]**	0.430 [0.263, 0.535]	0.283	13.22
	Second peak total	c1 + c2 KAM	2.991 [2.675, 3.433]	**0.122 [−0.047, 0.263]**		**0.036 [−0.015, 0.141]**	0.484	14.89
		c1 + c2KAM + c3 |KFM|	3.025 [2.659, 3.506]	**0.128 [−0.035, 0.267]**	**−0.060 [−0.240, 0.099]**	**0.027 [−0.031, 0.120]**	0.487	14.98
	Medial to total force ratio (at second peak)	c1 + c2 KAM	0.513 [0.497, 0.529]	0.066 [0.059, 0.074]		0.858 [0.803, 0.888]	0.024	3.65
		c1 + c2KAM + c3 |KFM|	0.510 [0.494, 0.525]	0.065 [0.058, 0.074]	**0.006 [−0.004, 0.013]**	0.859 [0.801, 0.887]	0.024	3.65
First and second peaks stance phase	First and second medial	c1 + c2 KAM	1.584 [1.435, 1.769]	0.163 [0.102, 0.212]		0.203 [0.108, 0.297]	0.339	16.73
		c1 + c2 KAM + c3 |KFM|	1.581 [1.438, 1.759]	0.209 [0.141, 0.267]	−0.063 [−0.100, −0.023]	0.247 [0.138, 0.334]	0.330	16.28
	First and second total	c1 + c2KAM	2.906 [2.653, 3.205]	**−0.058 [−0.153, 0.023]**		**0.003 [−0.008, 0.051]**	0.595	21.64
		c1 + c2KAM + c3 |KFM|	2.932 [2.704, 3.179]	**0.066 [−0.040, 0.169]**	−0.168 [−0.230, −0.108]	0.150 [0.053, 0.240]	0.549	19.96
	Medial to total force ratio (at first and second peak)	c1 + c2KAM	0.489 [0.464, 0.510]	0.093 [0.085, 0.104]		0.714 [0.648, 0.759]	0.063	8.82
		c1 + c2KAM + c3 v	0.489 [0.465, 0.510]	0.085 [0.074, 0.099]	0.011 [0.003, 0.018]	0.727 [0.661, 0.769]	0.062	8.37
Complete stance phase (impulse)	Medial	c1 + c2 KAMi	0.608 [0.528, 0.697]	0.279 [0.208, 0.343]		0.581 [0.437, 0.671]	0.093	10.22
		c1 + c2 KAMi + c3 KFMi	0.463 [0.343, 0.605]	0.263 [0.199, 0.322]	0.153 [0.053, 0.258]	0.631 [0.488, 0.706]	0.087	9.89
	Total	c1 + c2 KAMi	1.180 [1.040, 1.336]	0.117 [−0.001, 0.224]		**0.071 [−0.010, 0.196]**	0.152	11.62
		c1 + c2 KAMi + c3 KFMi	0.912 [0.681, 1.150]	**0.088 [−0.024, 0.186]**	0.283 [0.125, 0.444]	0.217 [0.053, 0.345]	0.140	10.93
	Medial to total force ratio	c1 + c2 KAMi	0.531 [0.508, 0.553]	0.152 [0.132, 0.174]		0.831 [0.762, 0.868]	0.027	3.90
		c1 + c2 KAMi + c3 KFMi	0.559 [0.521, 0.593]	0.155 [0.133, 0.178]	**−0.030 [−0.061, 0.005]**	0.839 [0.767, 0.872]	0.026	3.70

Numbers in bold represent changes that did not contribute significantly to the model or non-statistically significant R^2 values. All other changes were significant at $\alpha = 0.05$. 95% confidence intervals for the coefficients, c1, c2 and c3 based on 1000 bootstrap samples.

Finally, ΔKAM impulse was weakly associated with ΔmKCF to tKCF ratio (adjusted R^2 values of 0.32 and 0.40) for toe-in gait and wide-steps gait respectively (Table V).

Discussion

We investigated the relationships between the knee joint moments and the internal knee loading in people with medial KOA during steady-state walking. Moreover, we investigated the effects of toe-in and wide-steps gait on the KCF, and the effects of these modifications on the relationships between the external joint moments and internal joint forces. To the best of our knowledge, this is the first paper to report changes in KCF during gait modifications in KOA patients. Previous studies have reported effects of gait modifications on knee moments[17] or on KCF post-TKA[22,35] or in healthy controls[34,36]. We found that walking with a modified gait did not reduce the KCF compared to normal walking. However, medial to total KCF ratio was significantly reduced.

During normal walking, first peak KAM was statistically associated with first peak mKCF ($R^2 = 0.60$ [0.47, 0.68]), similar to the association reported post-ACL reconstruction[8]. Including first peak KFM increased the variance explained by the regression model by 13%, reiterating that KAM and KFM are both predictors of the mKCF[7,8]. The first peak KAM coefficient (0.239 [0.177, 0.282]) was more than twice that of the KFM coefficient (0.102 [0.064, 0.145]). Hence, for a given reduction in first peak KAM of 10%, KCF will be reduced only if the increase in KFM is less than 23.43 [19.44, 27.6]%. Studies investigating effects of gait modifications often focus exclusively on KAM without considering KFM. Accordingly, a reduction in KAM with a concurrent increase in KFM means that the mKCF will not necessarily be reduced. Indeed, data from an instrumented knee prosthesis during medial thrust gait showed that even with a reduction in KAM of 32% during medial thrust gait, mKCF was not significantly reduced[22].

At the second peak, KAM and mKCF were less well associated 0.44 [0.29, 0.55], suggesting that second peak KAM is a poor predictor of second peak mKCF. KFM was not a significant predictor of mKCF, coefficient of 0.00 [−0.100, 0.083]. The weak relationship between KAM, KFM and the internal KCF at the second peak may be explained by a combination of high co-contraction between the quadriceps and the plantar flexor muscles at the second peak and a sensitivity of the model to small errors in the moment arm of the rectus femoris. Interestingly, mKCF and tKCF are both higher at the second peak than at the first while KAM and KFM are both higher at the first. This discrepancy is likely due to the co-contraction of the knee flexors and extensors, which is represented in the musculoskeletal model but not in the external joint moments. In a study of nine subjects with instrumented knee replacements, second peak mKCF was higher than first peak in five subjects, whereas second peak KAM was higher only in one subject. Given this, and the results from our models, future studies should be cautious about interpreting second peak KAM as a predictor (or surrogate measure) of KCF.

In this study, first peak mKCF during walking with modified gait was not significantly reduced, despite a significant reduction in KAM. This is in contrast with significant reductions reported by Schlotman (2016)[37] and Koblauch *et al.* (2013)[34]. In the latter study[34] the change in FPA was over 25°, an unsustainable FPA change for KOA patients during activities of daily living. Furthermore, the reductions in the mKCF were accompanied by a concurrent 25% increase in the tKCF increasing lateral KCF by 125%, a potentially damaging increase. Our finding corroborates that of Walter *et al.* (2010)[22]; changes in KAM are not necessarily reflected in changes in the mKCF. Based on this, we suggest that there is currently insufficient evidence for using gait modifications as a clinical intervention since we did not find clinically significant changes in KCF and the disease modifying effect remains unknown.

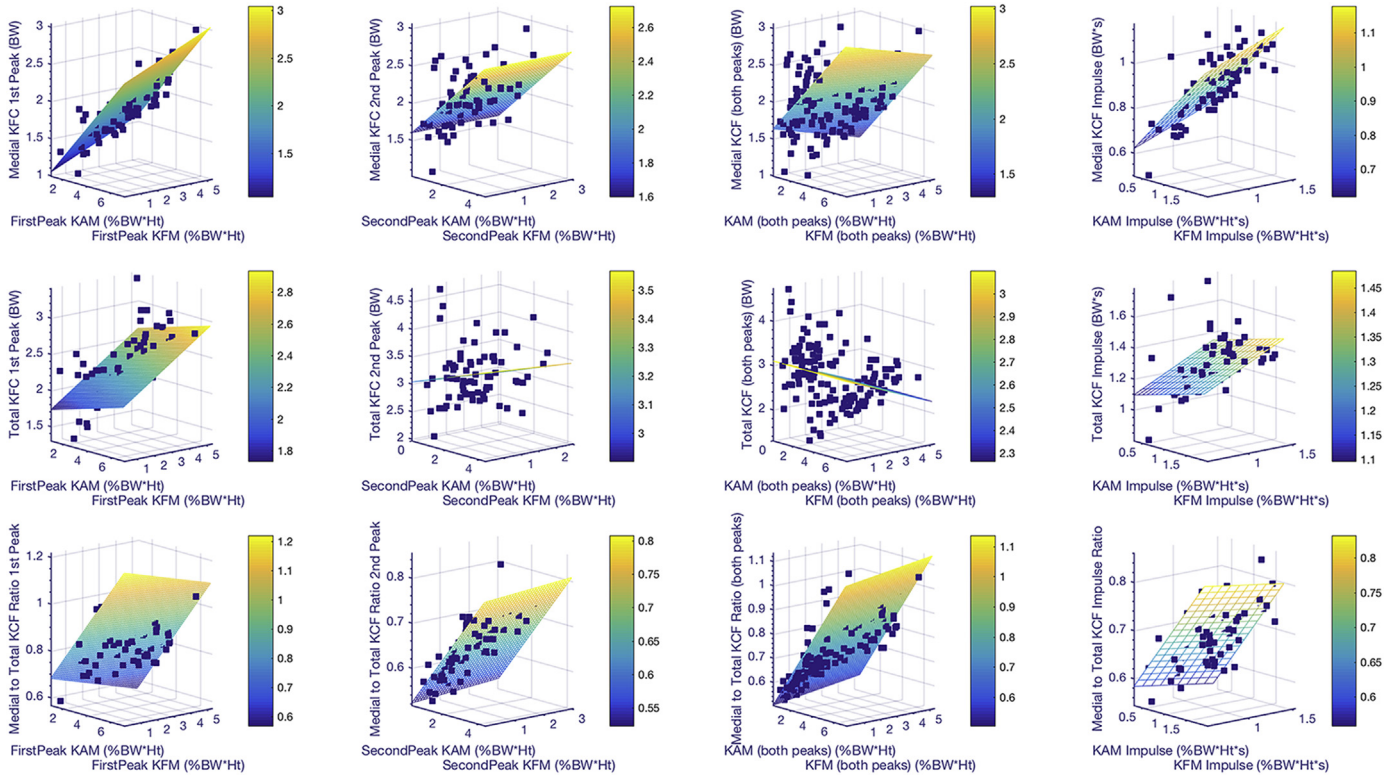

Fig. 1. Regression models for medial knee contact force (KCF) (top), total KCF (middle) and medial (mKCF) to total KCF (tKCF) ratio (bottom), as a function of the external knee joint moments. Left – first peak, centre left-second peak and centre right-both peaks and right-impulse.

Table III
Peak and impulse of external joint moments and internal knee contact forces and ratio of medial to total contact force; Mean (standard deviations) or Median (inter-quartile range, IQR)

		Normal walking/baseline	Toe-in gait	Wide Steps gait	*P* (group level)
Knee moment (%BW*Ht or %BW*Ht*s)	Adduction first peak	*3.42 (0.90)*	***3.27 (1.29)***†	***3.26 (1.11)***†	**0.002**
	Adduction second peak	2.50 (0.79)	2.47 (0.78)	2.54 (0.81)	0.794
	Adduction impulse	1.10 (0.40)	1.07 (0.40)	1.10 (0.40)	0.143
	Flexion first peak	*3.59(1.62)*	*3.24 (1.62)*	*3.69 (1.98)*	0.075
	Flexion impulse	1.06 (0.23)	1.05 (0.23)	1.05 (0.23)	0.120
Contact force (BW or BW*s)	Medial first peak	1.89 (0.36)	1.89 (0.37)	1.85 (0.35)	**0.019**
	Medial second peak	2.10 (0.38)	**2.03 (0.33)**‡	2.11 (0.38)	**0.002***
	Total first peak	2.29 (0.36)	2.36 (0.42)	2.29 (0.38)	**0.019**
	Total second peak	3.18 (0.44)	**3.03 (0.36)**‡	3.23 (0.50)	**<0.001***
	Medial impulse	0.90 (0.15)	0.88 (0.14)	0.89 (0.14)	0.108
	Total impulse	1.28 (0.14)	1.27 (0.13)	1.28 (0.15)	0.619
Medial to total force ratio	First peak	0.83 (0.10)	**0.81 (0.10)**‡	**0.81 (0.10)**‡	**<0.001***
	Second peak	0.66 (0.06)	**0.67 (0.07)***	0.65 (0.07)	**0.001**
	Impulse	0.70 (0.07)	0.69 (0.01)	0.70 (0.01)	0.196

Significant results shown in bold.
Results in italics are median and inter-quartile range (i.e. non-parametric testing). All others are mean and standard deviation.
* After Greenhouse Geisser correction for non-spherical data.
† Significant difference in post-hoc pairwise testing compared to normal walking at $\alpha = 0.05$, after Sidak correction for multiple tests.
‡ Significant difference in post-hoc pairwise testing compared to normal walking at $\alpha = 0.001$, after Sidak correction for multiple tests.

Despite no significant reduction in first peak mKCF during modified gait walking, the ratio of mKCF to tKCF decreased significantly ($P < 0.001$), albeit by a small amount. Redistributing the load towards the lateral compartment may be beneficial since the lateral cartilage tends to be thicker than the medial[38]. In severe KOA subjects, thinner medial compartment cartilage is associated with higher KAM values[39]. This suggests that, unlike in young, healthy controls[38], the cartilage in the knees of people with (severe) KOA do not respond positively to the loads placed on it. Hence, a reduction in medial compartment load may reduce cartilage thinning and potentially slow disease progression.

Surprisingly, next to a decrease in first peak KAM, second peak mKCF and tKCF decreased during toe-in gait, albeit a smaller reduction than reported during toe-out gait[36]. However, there was no significant change in the second peak KAM, reiterating that second peak KAM is a poor surrogate measure for second peak KCF. The reduction in second peak tKCF likely results from a reduction in the gastrocnemius force, which is strongly correlated with the peak KCF[40]. Reducing the gastrocnemius force may not be a clinically recommendable option for gait retraining considering the important role of the gastrocnemius in power generation in terminal stance.

Despite KAM reductions during toe-in gait, mKCF did not decrease since changes in mKCF are dependent on both tKCF and KAM (equations (1) and (2)). This result suggests a limited clinical effect of toe-in gait on the mKCF and tKCF. Post-hoc analysis of the individual muscle activity predicted by the model (Figure S3 in Appendix C) and

Table IV
Regression equations with corresponding R^2 and RMS errors for fitting Δ peak medial knee contact force and Δ peak medial knee contact to total contact force as a function of Δ peak knee adduction moment (KAM) and Δ peak knee flexion moment (KFM)

			Regression equation	c1 [95% CI]	c2 [95% CI]	c3 [95% CI]	Adj. R^2 [95% CI]	RMS error (BW)
Δ peak Medial Knee Contact Force	First peak	Change between normal and toe-in gait	c1 + c2 ΔKAM	−0.044 [−0.071, −0.015]	0.345 [0.243, 0.436]		0.540 [0.380, 0.641]	0.111
			c1 + c2 ΔKAM + c3 Δ|KFM|	−0.048 [−0.074, −0.025]	0.269 [0.173, 0.337]	0.111 [0.077, 0.156]	0.740 [0.625, 0.795]	0.083
		Change between normal and wide steps gait	c1 + c2 ΔKAM	−0.043 [−0.072, −0.019]	0.380 [0.241, 0.517]		0.530 [0.369, 0.632]	0.101
			c1 + c2 ΔKAM + c3 Δ|KFM|	**0.013 [−0.012, 0.036]**	0.239 [0.152, 0.342]	0.151 [0.096, 0.194]	0.804 [0.713, 0.846]	0.066
	Second peak	Change between normal and toe-in gait	c1 + c2 ΔKAM	0.080 [0.049, 0.110]	0.193 [0.081, 0.275]		0.215 [0.065, 0.358]	0.123
			c1 + c2 ΔKAM + c3 Δ|KFM|	0.079 [0.047, 0.110]	0.192 [0.079, 0.277]	**0.000 [−0.065, 0.038]**	0.200 [0.032, 0.334]	0.124
		Change between normal and wide steps gait	c1 + c2 ΔKAM	**−0.020 [−0.070, 0.022]**	0.261 [0.158, 0.401]		0.244 [0.087, 0.386]	0.167
			c1 + c2 ΔKAM + c3 Δ|KFM|	**−0.022 [−0.069, 0.21]**	0.263 [0.159, 0.404]	**0.030 [0.005, 0.069]**	0.278 [0.093, 0.408]	0.163
Δ ratio of peak Medial Knee Contact Force to Total Contact Force	First peak	Change between normal and toe-in gait	c1 + c2 ΔKAM	0.014 [0.006, 0.021]	0.060 [0.037, 0.084]		0.315 [0.146, 0.451]	0.030
			c1 + c2 ΔKAM + c3 Δ|KFM|	0.015 [0.009, 0.022]	0.079 [0.059, 0.101]	−0.027 [−0.040, −0.016]	0.551 [0.379, 0.644]	0.025
		Change between normal and wide steps gait	c1 + c2 ΔKAM	0.009 [0.003, 0.017]	0.062 [0.029, 0.099]		0.290 [0.124, 0.428]	0.027
			c1 + c2 ΔKAM + c3 Δ|KFM|	**−0.004 [−0.011, 0.004]**	0.096 [0.064, 0.120]	−0.036 [−0.048, −0.021]	0.616 [0.460, 0.696]	0.020
	Second peak	Change between normal and toe-in gait	c1 + c2 ΔKAM	−0.011 [−0.015, −0.006]	0.076 [0.065, 0.095]		0.721 [0.607, 0.783]	0.016
			c1 + c2 ΔKAM + c3 Δ|KFM|	−0.011 [−0.015, −0.006]	0.076 [0.064, 0.095]	0.001 [−0.003, 0.008]	0.717 [0.592, 0.777]	0.016
		Change between normal and wide steps gait	c1 + c2 ΔKAM	**−0.001 [−0.005, 0.004]**	0.071 [0.055, 0.085]		0.715 [0.599, 0.779]	0.017
			c1 + c2 ΔKAM + c3 Δ|KFM|	**−0.001 [−0.005, 0.004]**	**0.071 [0.055, 0.086]**	**−0.002 [−0.005, 0.000]**	0.719 [0.595, 0.778]	0.017

Numbers in bold represent changes that did not contribute significantly to the model or non-statistically significant R^2 values. All other changes were significant at $\alpha = 0.05$. 95% confidence intervals for the coefficients, c1, c2 and c3 based on 1000 bootstrap samples.

Table V
Regression equations with corresponding R^2 and RMS errors for fitting Δ peak medial knee contact force impulse as a function of ΔKAM impulse (ΔKAMi) and ΔKFM impulse (ΔKFMi)

	Regression Equation	c1 [95% CI]	c2 [95% CI]	c3 [95% CI]	Adj. R^2 [95% CI]	RMS error (BW*s)
Change between normal gait and toe-in gait	c1 + c2 ΔKAMi	**0.008** [0.000, 0.016]	0.193 [0.103, 0.279]		0.317 [0.148, 0.453]	0.030
	c1 + c2 ΔKAMi + c3 ΔKFMi	0.008 [0.000, 0.016]	0.188 [0.104, 0.256]	**0.023 [−0.079, 0.114]**	0.313 [0.124, 0.440]	0.030
Change between normal gait and wide steps	c1 + c2 ΔKAMi + c3 ΔKFMi	**0.001 [−0.007, 0.09]**	0.253 [0.155, 0.348]		0.403 [0.231, 0.528]	0.033
	c1 + c2 ΔKAMi + c3 ΔKFMi	**0.004 [−0.004, 0.013]**	0.249 [0.161, 0.336]	0.139 [0.063, 0.226]	0.502 [0.322, 0.604]	0.031

Numbers in bold represent changes that did not contribute significantly to the model or non-statistically significant R^2 values. All other changes were significant at $\alpha = 0.05$. 95% confidence intervals for the coefficients, c1, c2 and c3 based on 1000 bootstrap samples.

of the electromyographic (EMG) profiles recorded over the knee-spanning muscles (Fig. S4) revealed only small changes in these profiles between conditions with considerable variation between subjects. Changes in muscle forces may be attributable to compensatory movements such as increasing knee flexion, which was commonly observed during walking with a modified gait pattern. An increase in the knee flexion and hence knee flexion moment increases activation of the muscles crossing the knee which may increase the tKCF. Through training, it may be possible to train the desired gait modification without coincident compensations such as increased knee flexion.

Although we did not find significant reductions in the mKCF during modified gait walking, a moderate statistical association existed between the *change* in KAM and the *change* in mKCF for both toe-in gait and wide-steps gait at the first peak ($R^2 = 0.54$ and 0.53). However, according to our model a 10% reduction in first peak KAM would yield only a 4% reduction in first peak mKCF. Consequently, for a 10% reduction in first peak mKCF, a 29% reduction KAM would be required. Achieving this would require a greater modification of the gait pattern, which would be likely unsustainable. Change in KFM also contributed strongly to the change in mKCF for both modified gait patterns (coefficients of 0.27 for KAM and 0.11 for KFM during toe-in gait and 0.24 to 0.15 during wide-steps gait). A 10% reduction in KAM would, therefore, be negated by a 25% increase in KFM during toe-in gait and a 16% increase during wide-steps gait. Gait modifications that reduce both KAM and KFM may therefore be preferable to modifications reducing KAM only. Creaby (2015)[7] proposed a combination of stiff knee gait to reduce KFM with trunk lean to reduce KAM, but this has yet to be tested in practice. Furthermore, this strategy may increase knee stiffness and co-contraction, and therefore increase KCF.

Focusing on the internal KCF does not provide the full picture; the KCF does not provide information about the cartilage stresses – ultimately the parameter we are trying to change. A recent study showed that alongside higher peak KCF, contact pressures are increased in established KOA[41]. To assess changes in cartilage loading, finite element modeling and imaging of the knee joint using magnetic resonance imagine (MRI) is required[42]. A recent case study using subject-specific modeling and investigating effects of gait modifications found that changes in KAM were not correlated with changes in the medial contact pressures[43]. Devices, that can replicate the knee joint movement *in vitro*, such as that designed by van de Bunt *et al.* (2017)[44] may also provide valuable insight into the effects of gait modifications on the cartilage.

We must bring attention to the limitations of this work. First, aside from gross scaling, the musculoskeletal model used in this study was not personalized to the individual. Furthermore, we did not consider any neural factors, not associated with altered kinematics and kinetics, meaning that the model does not represent the altered neural activation patterns shown in KOA patients[45]. We did not personalize the muscle parameters and we used a hinge joint to model the knee in the inverse dynamics calculations. However this approach has been shown to predict KCF with similar accuracy to a more complex model[16]. To improve estimated joint loads, including subject-specific morphology developed from MRI[46] or CT scans[47] and subject-specific maximum isometric strength for each individual muscle can be used. In the KOA population, there are often co-contractions between muscle groups[48,49] which are associated with increased disease progression[49]. These co-contractions may not be adequately represented in the model in this study.

We did not perform any correction for soft tissue artefacts. Future small-scale research studies using fluoroscopy to measure the bone movement are recommended to reduce reliance on skin mounted markers.

The regression models we present may have limited generalizability to the wider KOA population due to strict inclusion criteria for

this study[27]. We included only people with medial KOA since the intervention is only valid for people with medial KOA. Furthermore, the choice of linear regression analysis may be sub-optimal for representing the complex and non-linear behavior of the multi-body musculoskeletal system. Moreover, while we found statistically significant results, the effect sizes are unlikely to be clinically significant.

Finally, we assessed within-session changes in KCF and cannot extrapolate to long-term effects. Further work is needed to assess these effects, particularly since we hypothesize that tKFC may reduce with training time.

In conclusion, KAM was found to be a strong predictor of mKCF at the first peak during normal walking. Including KFM as a second predictor improved the relationship between the internal loading and the external moments. This suggests that the combination of KAM and KFM yields an improved surrogate measure of KCF, aiming to represent the cartilage loading, than KAM alone. At the second peak, the external moments are poor predictors of the mKCF. In this study, walking with toe-in or wide-steps gait modified first peak KAM, but did not reduce mKCF. However, the ratio of mKCF to tKCF, representing the distribution of the loading, was reduced. Changes in mKCF during modified gait were statistically associated with the changes in external moments at the first but not at the second peak. Future gait retraining studies should focus not only on reducing first peak KAM but also KFM to maximize the chances of reducing the medial contact force.

Contributions

1) The conception and design of the study, or acquisition of the data, or analysis and interpretation of the data. Conception and design of the study: RR, JvdN and JH. Acquisition of the data: RR, JvdN. Analysis and interpretation of the data: RR, MSA, JvdN.
2) Drafting the article or revising it critically for important intellectual content. Drafting of the article: RR, MSA, JvdN. Revising it critically for important intellectual content: MSA, JvdN, JH, RR.
3) Final approval of the version to be submitted: RR, MSA, JvdN, JH.

Competing interest statement

There are no competing interests to declare.

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Appendix A

The model used to predict the knee contact forces (KCF) in this manuscript was based a previously validated model. However, since the publication of the model in Lund *et al.*[28] some small bugs have been fixed and the muscle recruitment criterion updated to account for sub-divided muscles[16] to improve the predictions of the forces. In Fig. S1, we present a comparison of the measured KCFs and the predicted KCFs based on 3 subjects (years 3, 4 and 5) and 4 trials per subject from the Grand Challenge data set[50]. The strength of the knee flexors and extensors in the model used in the validation has been reduced by 35 % to match previous modeling assumptions for TKA patients[16, 28].

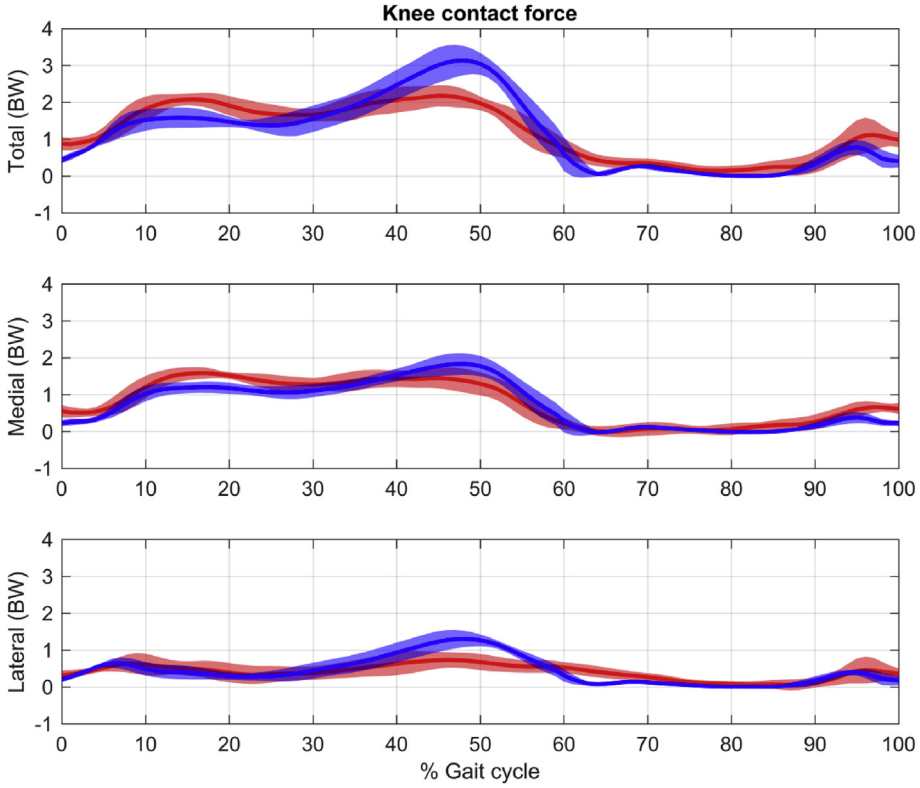

Fig. S1. Measured knee contact forces (KCF) in red versus predicted KCF in blue. Solid line: average over the 3 subjects and 4 trials each. Shaded area ± 1 std.

Table S1
Quantification of the prediction accuracy against the Grand Challenge data. The results are presented as mean (±1 std) over the 3 subjects and 4 trials each.

		Total	Medial	Lateral
R^2		0.75 (0.05)	0.78 (0.04)	0.42 (0.19)
RMS (BW)		0.52 (0.09)	0.31 (0.05)	0.32 (0.08)
Peak 1 (BW)	Predicted	1.72 (0.17)	1.24 (0.14)	0.68 (0.12)
	Measured	2.20 (0.13)	1.66 (0.13)	0.74 (0.19)
	Error	0.48 (0.24)	0.43 (0.21)	0.23 (0.08)
Peak 2 (BW)	Predicted	3.19 (0.40)	1.86 (0.29)	1.35 (0.20)
	Measured	2.34 (0.25)	1.64 (0.26)	0.82 (0.21)
	Error	0.85 (0.32)	0.22 (0.11)	0.53 (0.30)

Appendix B

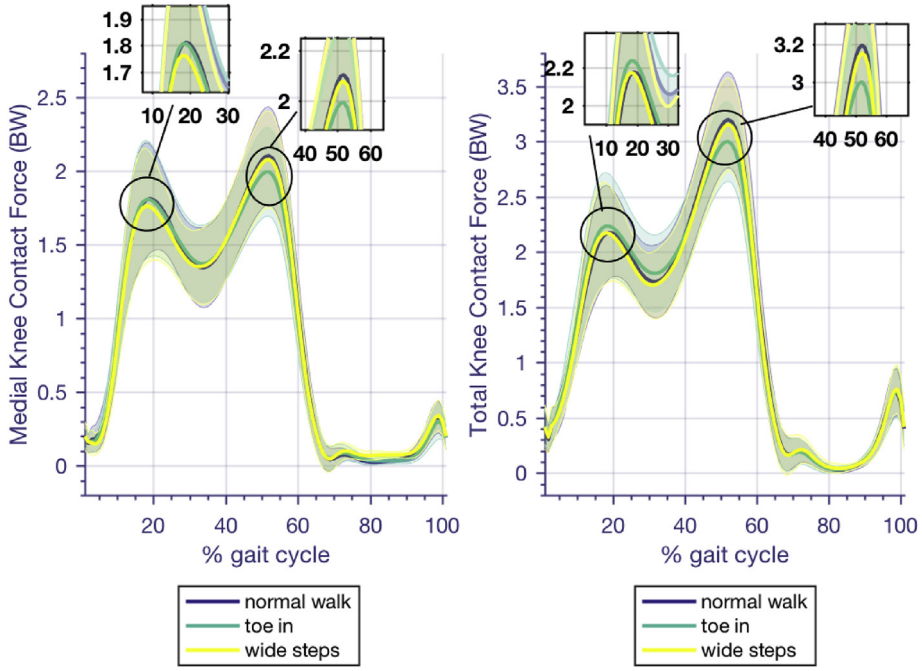

Fig. S2. Medial and total knee contact forces during normal walking, toe-in gait and walking with wider steps.

Appendix C

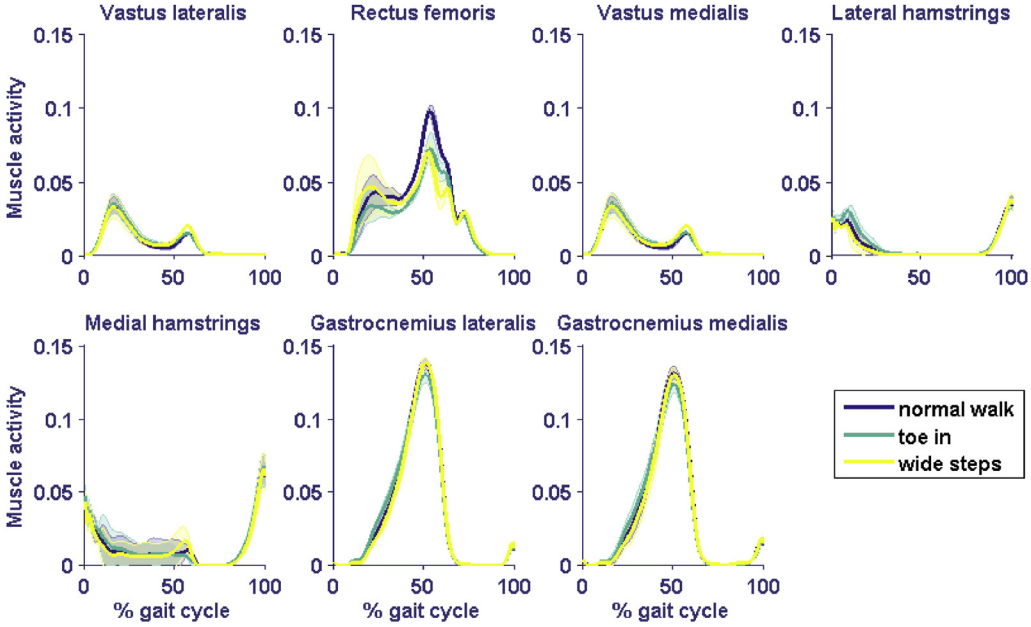

Fig. S3. Activity (mean ± standard deviation) of the knee spanning muscles calculated using the AnyBody model during normal walking, toe-in gait and wide steps gait. Note that the activity is defined as the force delivered by the muscle divided by the strength of the muscle (hence no units).

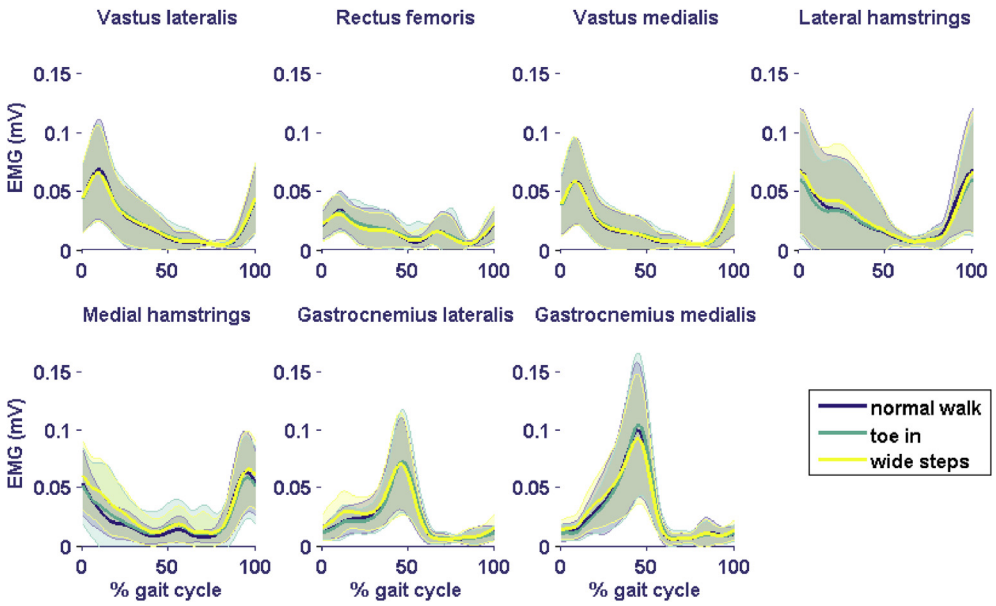

Fig. S4. EMG activity (mean ± standard deviation) of the knee spanning muscles during normal walking, toe-in gait and wide steps gait.

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