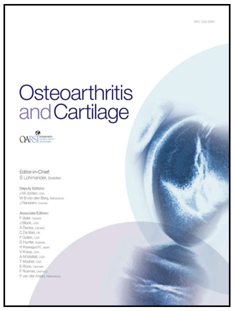

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Frontal plane knee alignment mediates the effect of frontal plane rearfoot motion on knee joint load distribution during walking in people with medial knee osteoarthritis

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Abstract

Objective: To examine the nature of differences in the relationship between frontal plane rearfoot kinematics and knee adduction moment (KAM) magnitudes

Design: Cross-sectional study resulting from a combination of overground walking biomechanics data obtained from participants with medial tibiofemoral osteoarthritis at two separate sites. Statistical models were created to examine the relationship between minimum frontal plane rearfoot angle (negative values = eversion) and different measures of the KAM, including examination of confounding, mediation, and effect modification from knee pain, radiographic disease severity, static rearfoot alignment, and frontal plane knee angle.

Results: Bivariable relationships between minimum frontal plane rearfoot angle and the KAM showed consistent negative correlations (r = -0.411 to -0.447), indicating higher KAM magnitudes associated with the rearfoot in a more everted position during stance. However, the nature of this relationship appears to be mainly influenced by frontal plane knee kinematics. Specifically, frontal plane knee angle during gait was found to completely mediate the relationship between minimum frontal plane rearfoot angle and the KAM, and was also an effect modifier in this relationship. No other variable significantly altered the relationship.

Conclusions: While there does appear to be a moderate relationship between frontal plane rearfoot angle and the KAM, any differences in the magnitude of this relationship can likely be explained through an examination of frontal plane knee angle during walking. This finding suggests that interventions derived distal to the knee should account for the effect of frontal plane knee angle to have the desired effect on the KAM.

Keywords: gait; knee adduction moment; osteoarthritis; mediation; rearfoot

Introduction

Investigations into the biomechanics of gait in people with knee osteoarthritis (KOA) have traditionally focused on factors local to the knee. A number of key biomechanical outcome measures unique to KOA – most commonly medial tibiofemoral involvement – have been identified, with the external knee adduction moment (KAM) – a surrogate for the distribution of load across the tibiofemoral joint – receiving the most attention. While the importance of outcomes such as the KAM has been established through links with disease-relevant features such as joint pain [1], as well as structural [2, 3] and clinical [4] disease progression, there is a growing body of literature suggesting that factors distal to the knee joint may also be important to consider to further our understanding of disease pathogenesis.

Emerging evidence points to an important role of foot symptoms and posture in the clinical and biomechanical features of KOA. Data from the Osteoarthritis Initiative indicate that 25% of people with KOA experience concomitant foot pain [5]. Using data from the same cohort, Paterson et al. also showed that in the 1,020 participants who were at risk for KOA, but were free of knee symptoms and radiographic involvement, the presence of foot pain at baseline significantly increased the odds of developing knee symptoms or painful radiographic KOA over the subsequent 4 years [6]. It would appear that people with a flat (planus) foot posture are particularly vulnerable to the symptomatic and radiographic characteristics of KOA. Data from the Framingham cohort indicate that older people with flat feet are more likely to report knee pain or to develop medial tibiofemoral cartilage damage [7]. This is important to note given that multiple studies have reported a higher prevalence of flat feet in people with KOA compared to healthy controls [8-10]. Taken together, these studies point to a strong need to consider foot posture in the study and treatment of people with KOA.

The potential link between KOA-relevant knee biomechanics and foot mechanics during gait has also been studied. Consistent with a higher prevalence of static flat foot posture in people with KOA described above, Levinger et al. reported that people with KOA exhibit more dynamic rearfoot eversion (a component of a flat foot posture) during walking than healthy controls [11]. Data from the same cohort also suggest that greater rearfoot eversion during gait is associated with lower KAM magnitudes in late stance [12]. These findings are consistent with the results from Chapman et al. who showed that increased rearfoot eversion during walking was predictive of which people with KOA would reduce the KAM with the use of lateral wedge insoles (LWIs) [13]. In contrast, Sawada et al. reported the opposite finding; that is, decreased rearfoot eversion was correlated with KAM reductions in people with neutral foot postures, determined statically when wearing LWIs [14]. Clarifying these important relationships are required to better guide KOA treatment approaches that rely on modification of foot posture or position, such as LWIs, to reduce KAM magnitudes, knee pain, and potential risk of OA progression.

One potential explanation for this apparent discrepancy in the existing literature is that the nature of these relationships differs based on certain clinical or biomechanical characteristics. Indeed, KAM magnitudes are known to be different across radiographic disease severities [15], and previous work has highlighted differences in the relationship between the KAM and knee joint pain based on radiographic disease severity [16, 17]. Unfortunately, previous studies examining rearfoot biomechanics in people with KOA have had relatively low sample sizes (less than that

70 participants) preventing any such exploratory analysis. Therefore, the purpose of the present study was to examine the relationship between rearfoot kinematics and KAM magnitudes across a number of different factors, including: disease severity, static foot posture, dynamic lower limb alignment, and knee joint pain. Confounding, effect modification, and mediation analyses were used to provide more in-depth assessment of this relationship whilst accounting for these different factors.

Methods

Participants

Data from this study were comprised from available data separately collected at two sites – University of Salford (UK) and the University of British Columbia (Canada) – from 2012-2019. Individuals from the community were recruited to participate in a number of clinical research studies, and the data presented herein were from baseline assessments before any intervention (if applicable) was delivered. In all cases, inclusion criteria included: age greater than 45 years; definitive evidence of mild or moderate tibiofemoral osteophytes on standing radiographs (and classified as Kellgren and Lawrence grade 2 and 3 [18]); and, self-reported knee pain lasting longer than six months and which had also occurred on most days of the month preceding testing. Primary exclusion criteria included: any history of lower limb joint replacement surgery; any lower limb surgery or procedure in the six months preceding testing; any condition other than KOA affecting lower limb function during gait; presence of inflammatory arthritis in any lower limb joint; body mass index (BMI) greater than 35 kg/m^2; and, an inability to walk unaided. In all instances, participants provided written informed consent, and ethical approval was provided by the relevant institutional Ethics Review Boards.

Data Collection

After demographic and disease history were obtained, participants completed self-report questionnaires to characterize OA symptoms using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [19]. Participants then underwent a three-dimensional gait analysis while barefoot and at a self-selected, preferred walking speed, along an approximately 10m long walkway. The knee with osteoarthritic signs, or in the case of bilateral knee OA, the more symptomatic knee, was selected as the study limb. The positions of retro-reflective skin markers common to both study sites included: unilaterally at the lumbosacral junction; and bilaterally at the anterior superior iliac spines, lateral femoral epicondyles, lateral malleoli, and heads of the second metatarsals. Finally, markers were placed bilaterally over the medial femoral epicondyles and malleoli, as well as the bases of the first and fifth metatarsals, during an initial static standing trial used to define segment orientations. Additional 4- marker clusters were affixed bilaterally over the lateral thighs and lateral shanks.

Kinematic data were collected using high-speed motion analysis infrared cameras at the sampling rate of either 100 Hz (Salford) or 120 Hz (UBC), while ground reaction force data were collected with the synchronized force platforms at the sampling rate of either 1000 Hz (Salford) or 1200 Hz (UBC). Five good trials with complete markerset data and one foot on one force plate were analyzed for each participant.

Data Analysis

All kinematic and kinetic data were analyzed using the same six-degrees of freedom biomechanical model within Visual 3D (C-Motion, Germantown, USA). All lower limb extremity segments were modelled as rigid bodies using available anthropometric parameters. Ankle and knee joint centres were calculated as the midpoints of the malleolar and femoral epicondyle markers, respectively. The hip joint centres were calculated based on published regression models that use the anterior and posterior iliac spine markers [20]. Segment coordinate systems were created using markers defining the segment dimensions and tracked using the skin mounted markers for pelvis and foot, as well as marker clusters for shank and thigh. The segment coordinate system of the rearfoot was defined in the horizontal plane of the laboratory. Joint kinematics were calculated using an XYZ Cardan sequence, and represented as the distal segment relative to the proximal segment (in the case of rearfoot angle, it was calculated relative to the tibia). All joint coordinates and ground reaction force data were first filtered (6Hz for kinematics, 25Hz for kinetics) using a recursive lowpass Butterworth fourth-order digital filter, after which joint kinetics were calculated using inverse dynamics, as described previously [13]. Joint moments were expressed as external moments, resolved to the proximal segment (flexion, adduction and internal rotation were denoted as positive), and normalized to body mass (Nm/kg), while the knee adduction angular impulse reflected the amount of time during stance (Nm/kg * s).

The following biomechanical outcomes (known to be relevant in the knee OA gait literature) were identified for each walking trial, and participant averages were obtained as the mean value across five trials: walking velocity, peak KAM in the first 50% of stance (early stance peak), KAM at 50% of stance, peak KAM in the last 50% of stance (late stance peak), KAM impulse (area under KAM-time curve), average frontal plane knee angle from 30-70% of stance, frontal plane rearfoot angle at initial contact, and minimum frontal plane rearfoot angle. Static rearfoot angle in the frontal plane relative to the global frame of reference was calculated for each participant during the initial static standing trial, based on the relative orientation of the medial and lateral calcaneus markers.

Statistical Analysis

A multi-step process was used to examine the extent of the association between frontal plane rearfoot motion and the KAM. First, we used linear regression with minimum frontal plane rearfoot angle regressed on to each of the four KAM variables separately (early stance KAM, KAM at 50% of stance, late stance KAM, and KAM impulse) (Model 1 for each KAM variable). We also included an indicator variable in each of these initial models to denote the site origin of each data point (University of Salford or University of British Columbia). Next, we repeated these analyses with the inclusion of other variables (height and walking velocity) that might explain variance in KAM data (Model 2 for each KAM variable). If either of these variables explained significant amounts of variance ($p<0.05$) in a given KAM variable, they remained in subsequent models.

We then assessed the potential impact of the following four target variables on the relationship between minimum frontal plane rearfoot angle and KAM outcomes (Model 3 for each KAM variable): WOMAC pain, KL grade, static frontal plane rearfoot angle, and frontal plane knee angle. Since WOMAC pain, KL grade, and static frontal plane rearfoot angle were not expected to be part of the causal pathway between minimum frontal plane rearfoot angle and the KAM during gait, we examined for confounding by comparing the beta coefficients for minimum frontal plane rearfoot angle with and without the inclusion of each of these three target variables. Operational confounding was defined as a change in the rearfoot angle beta coefficient of more than 10% [21].

In contrast, the role of frontal plane knee angle during gait was considered to be part of this causal pathway. Therefore, we performed a mediation analysis for each of the KAM variables using a Baron and Kenny approach, with coefficients calculated using maximum likelihood regression modeling. Direct, indirect, and total effects were evaluated to determine whether frontal plane knee angle was a partial or complete mediator of the relationship between minimum frontal plane rearfoot angle and KAM (Figure 1). Partial mediation was defined by a significant indirect and direct effect, while complete mediation was defined by a significant indirect but nonsignificant direct effect, with statistical significant set to $p<0.05$ for each of these [22]. Finally, we tested for effect modification for each of the four target variables by creating interaction terms between each target variable and minimum frontal plane rearfoot angle, and then including them in a final model (Model 4 for each KAM variable). The presence of effect modification was indicated by a significant p-value ($p < 0.05$) of the interaction term in these models. In the event of significant effect modification, a tertile-based approach was used to visually inspect the nature of this effect. Specifically, the dataset was split into equal tertiles based on the target variable, and the bivariable correlation between minimum frontal plane rearfoot angle and the KAM was computed for each tertile.

Regression diagnostics were conducted on all models using residual analysis, Quantile-Quantile Plots (Q-Q plots) and Shapiro-Wilk for normality, and multicollinearity to ensure that the assumptions for linear modeling were satisfied. Finally a number of sensitivity analyses were conducted: first, all modeling was re-run using data from each site (UBC or Salford) separately and removing the indicator (site) variable from the models, and compared against the models using the full, combined dataset; second, all analyses were re-run using KAM data that were in raw Nm units, rather than divided by body mass. For these analyses, body mass was included as a forced covariate in the multiple regression modeling on raw KAM data. Finally, all analyses were re-run using the values of frontal plane knee and rearfoot angles at the times of early stance KAM peak, KAM at 50% of stance, and late stance KAM peak. All statistical analyses were conducted using Jamovi version 1 [23].

This study was a secondary analysis of combined available data (n=226) from the two sites. For the mediation analysis, a large effect size of the mediator variable (frontal plane knee angle) on the KAM variables was assumed based on previous literature [24], with a medium effect between frontal plane rearfoot and knee angles (based on the moderate bivariable correlation observed in the present study). As a result, our 226 participants exceeds the minimum requirement (n=204) to detect complete mediation (ie. $\tau' = 0$), based on published sample size requirements [25].

Results

Participant demographic information is summarized in Table 1. Although the magnitudes of the differences were small, there were a number of demographic, clinical, and biomechanical differences when comparing the samples from both sites.

A statistically significant negative bivariable relationship existed between the minimum frontal plane rearfoot angle and all KAM outcomes (r = -0.411 – -0.447); that is, greater rearfoot eversion was associated with higher KAM magnitudes, regardless of the specific KAM measure (Figure 2). When examining the potential influence of height and gait velocity, these two variables explained additional variance only in the models predicting KAM at 50% of stance and KAM impulse ($p < 0.05$). Accordingly, height and velocity remained in subsequent models as covariates for these two KAM outcomes.

When examining the effect of WOMAC pain, KL grade, static frontal plane rearfoot angle, and on the relationship between minimum frontal plane rearfoot angle and the KAM, none of these variables were found to be confounders or effect modifiers in this relationship (Supplementary Tables 1-3).

For the frontal plane knee angle mediation analysis, there was a statistically significant total effect in all measures of the KAM ($p<0.001$) (Table 2). While the indirect effects were all statistically significant ($p<0.001$), none of the direct effects were ($p>0.195$), indicating complete mediation of the relationship between minimum frontal plane rearfoot angle and KAM. Indeed, while minimum frontal plane rearfoot angle still contributed significantly ($p=0.042$) to the early stance KAM model in the presence of frontal plane knee angle, it did not contribute any significant portion to any of the other KAM models ($p>0.380$) (Table 3). Frontal plane knee angle was also found to be an effect modifier in the relationship between minimum frontal plane rearfoot angle and late stance KAM peak (interaction term: $p=0.021$) and KAM impulse (interaction term: p = 0.045), and almost for early stance KAM peak (interaction term: p = 0.076). (Table 3, Figure 3).

When comparing models using the combined dataset, or each dataset individually (without the indicator (site) variable), no differences between sites in direction (positive or negative), or statistical significance, of the beta coefficients were observed for Models 1 or 2. While the tests for confounding variables (Model 3) did not differ in the overall conclusions, KL grade showed mild confounding in the UBC data set only, while WOMAC pain was not a confounder in either individual data set. Additionally, tests for effect modification (Model 4) of the frontal plane knee angle and KL grade were only significant in the UBC data set. No other differences were observed for any of the mediation or effect modification models.

Only subtle differences in our findings were observed based on the other sensitivity analyses. For example, when using raw early stance peak KAM data (in Nm) and using body mass a covariate (Supplementary Table 4), minimum frontal plane rearfoot angle was no longer a significant predictor (p=0.086 vs. p=0.042)) in the final model (Model 4), however there were no changes to the mediation analyses. When using frontal plane knee and rearfoot data at the time of KAM peaks, no changes in the role of frontal plane rearfoot kinematics were observed in the multiple regression modelling (Supplementary Table 5), while frontal plane knee angle was now a partial (rather than complete) mediator of the relationship between frontal plane rearfoot angle and the early stance KAM peak (Supplementary Table 6).

Discussion

Findings from this study suggest that there is little direct relationship between frontal plane rearfoot motion and our surrogate of the distribution of load across the tibiofemoral joint, the KAM. While we did observe a statistically significant bivariate correlation between rearfoot motion and the KAM, this relationship became non-existent when examining the mediating role of dynamic frontal plane knee alignment during walking. As a result, it does not appear that frontal plane rearfoot angle has any independent association with the KAM, which suggests that interventions that aim to reduce the KAM should not primarily target rearfoot biomechanics.

Our data shed light on previous research which has shown contradictory findings related to the role of rearfoot motion in tibiofemoral joint load distribution. Early research supported the notion that greater rearfoot eversion was directly associated with less medial knee joint load (as evidenced by lower KAM magnitudes), in cross-sectional designs [12], and that individuals with more available rearfoot eversion during natural walking are more likely to reduce KAM magnitudes with LWIs [13]. However, this association was not consistent, as Levinger et al [12] reported different associations (in magnitude or direction) between rearfoot eversion and the KAM depending on the frame of reference (global or anatomical) or KAM outcome (early stance peak vs. late stance peak). It is important to note that rearfoot alignment does not represent fully the static or dynamic posture of the foot, and thus our findings should only be considered with respect to rearfoot biomechanics. Future research investigating the relationships between different components of foot posture and knee biomechanics is warranted.

More recent research has shown that the relationship between rearfoot motion and the KAM may not be consistent across all individuals. Buldt et al. [26] reported no statistically significant differences in KAM magnitudes among groups of individuals similarly categorized by the Foot Posture Index [27], and also reported no correlation (r = 0.04) between rearfoot eversion and the early stance KAM peak. Using LWIs as a model, Sawada et al. reported different changes in the KAM based on foot posture in both healthy individuals [28] and those with knee OA [14]. Finally, Koshino et al [29] reported that rearfoot kinematics in healthy individuals may be more closely coupled to hip kinematics than knee kinematics during walking. It is likely that factors such as frontal plane knee alignment played a role in these discordant findings. Taken together with our current findings, there does not appear to be a consistent relationship between rearfoot motion and tibiofemoral joint load distribution across all individuals, and other factors (especially frontal plane knee angle, or whether walking was assessed barefoot or shod) are important to consider. Therefore, differences in dynamic alignment distributions across samples, or shod/unshod testing differences may explain the discrepancies seen in the literature.

Frontal plane knee angle was found to be both a mediator and effect modifier in the current study, supporting previous reports of static lower limb alignment mediating changes in KAM magnitudes [30]. Data from the current study show a moderate correlation between minimum frontal plane rearfoot angle and frontal plane knee angle (r = 0.525; 95% CI: 0.424, 0.614), such that people with more rearfoot eversion also exhibited more knee adduction/varus. This finding provides further evidence of a mediating effect of lower limb alignment on the relationship between rearfoot kinematics and KAM magnitudes. Varus alignment is known to have strong associations with KAM magnitudes [24], as well as the risk of knee OA progression [31]. In fact, lower limb alignment has been shown to explain the majority of variance in KAM magnitudes [32]. This is due to the finding that the relative orientation between the ground reaction force and the knee joint centre (i.e. the lever arm) is more closely related to the KAM than the magnitude of external load (i.e. the ground reaction force) [33]. It is unlikely that the changes in the orientation of the calcaneus alone will significantly alter either the lever arm or ground reaction magnitude.

Our findings have important implications for the design and testing of foot-based interventions aiming to reduce KAM magnitudes. The magnitude of the change in rearfoot eversion likely does not contribute to reductions in the KAM, and that changes in rearfoot position with these interventions are a consequence of the approach rather than a mechanism for KAM reduction. Indeed, while Chapman et al [13] reported that individuals with knee OA who exhibited more rearfoot eversion during normal, shod walking were more likely to experience KAM reductions with LWIs, there was no statistically significant correlation between the changes measured in these variables. Instead, it is likely that any KAM reductions with interventions such as LWIs are produced through alterations in lower limb alignment or centre of pressure position that will decrease the lever arm. Studies investigating LWI mechanisms [14, 28, 34] show a combination of a lateralized centre of pressure and less varus lower limb alignment, with only small increases in rearfoot eversion. Further, Sawada et al [14] reported that individuals who could lateralize the centre of pressure with LWIs were more likely to reduce the KAM, independent of rearfoot static or dynamic posture.

Given that some have suggested that large amounts of eversion may increase the risk of foot pain or lower limb injury [35], and with the known associations between knee OA and foot pain [5, 6], treatments can still effectively reduce KAM magnitudes while normalizing foot mechanics. In fact, LWIs that incorporate arch supports to normalize rearfoot motion can still reduce the KAM

[36, 37] and may, in fact, improve knee pain to a greater extent than LWIs alone [38]. More research in this area is needed to optimize knee biomechanics and OA symptoms, while ensuring that foot mechanics are considered.

A primary innovation and strength of this study is the combination of data from different laboratories to create a very large dataset that is unique in knee OA gait biomechanics studies. Similarities in inclusion/exclusion criteria and data collection parameters permitted the analysis of data using a single biomechanical model and approach. Any small differences in the magnitude of some variables was countered by the overall large sample size, and also served to provide more conservative estimates of the relationships we investigated. When data were examined separately, small differences in the models were found (for example, confounding of KL grade or WOMAC pain). Importantly, the primary finding of our study – the mediating effect of frontal plane knee angle – was consistent between datasets. That being said, subtle differences in certain data collection parameters (for example, motion analysis equipment or site-specific sample demographics), must still be acknowledged.

Limitations of this study include the omission of a full foot analysis that would permit the examination of forefoot kinematics, as has been done previously [12]. Further, the use of a clinical measure of foot posture prevented a more thorough analysis of the role of static foot posture in knee OA gait. Additionally, WOMAC pain levels in our sample were relatively mild. It is unknown whether the relationship among variables reported in the current study would have been different in different groups of individuals such as healthy individuals, or in individuals with greater amounts of pain who would likely exhibit compensatory gait characteristics in response to the pain. Indeed, pain was found to be a small statistical confounder in the association between minimal frontal plane rearfoot angle and the KAM peak in early stance. Both datasets were largely populated by knees with KL grades 2 and 3, so generalizing these findings to more severe structural knee OA should be done with caution. Finally, we chose to report and analyze frontal plane knee and rearfoot angles as singular values (mean or peak, respectively), rather than across different time points (for example, magnitudes occurring at the same times as KAM peaks, or at 50% of stance) to minimize the number of analyzed variables for ease of interpretation, and to improve the clinical applicability of our findings. However, as indicated above, there were no meaningful changes to any of our findings when time-matched kinematic data were used instead of peak values. Our current findings support the involvement of frontal plane knee angle, as a whole, in the relationship between frontal plane knee kinetics and rearfoot kinematics, and justify further expansion of this work using different aspects of these variables, or by using sophisticated analysis techniques such as principal component analysis or statistical parametric mapping.

Overall, data from our large sample of barefoot walking gait biomechanics data collected from people with knee OA refute suggestions that rearfoot kinematics play a significant independent role in tibiofemoral load distribution. Instead, other factors, such as frontal plane knee angle, play a much more important role and mediate any relationship between rearfoot kinematics and knee joint load distribution. Accordingly, treatments aiming to reduce the KAM should not primarily focus on altering rearfoot kinematics; rather, ensuring that the centre or pressure is lateralized and/or minimizing the lever arm between the knee joint centre and ground reaction force vector, while also considering the effects on frontal plane knee alignment to have the desired effect on the KAM. Importantly, these findings provide an impetus to better understand the relationship between foot and knee biomechanics in this patient population. This may aid us in the optimization of foot-derived treatments that consider the entire lower limb kinetic chain as a strategy to improve both foot and knee symptoms and function.

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Author contributions

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Analysis and interpretation of the data: MAH, JMC, DTF, GEC, AL, AG, RKJ.

Drafting of the article: MAH.

Critical revision of the article for important intellectual content: JMC, DTF, GEC, AL, AG, RKJ.

Final approval of the article: MAH, JMC, DTF, GEC, AL, AG, RKJ.

Statistical expertise: MAH, JMC, DTF

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Conflict of interest

None

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Figure Headings

Figure 1. Conceptulization of the mediation analysis of frontal plane knee angle during gait in the relationship between minimum frontal plane rearfoot angle on the knee adduction moment. The analysis considers both the indirect effect (the component that acts through the mediator) and the direct effect (does not act through the mediator). Partial mediation was defined by a significant indirect and direct effect, while complete mediation was defined by a significant indirect but nonsignificant direct effect, with statistical significant set to p<0.05 for each of these.

Figure 2. Scatterplots showing the bivariable relationship between minimum frontal plane rearfoot angle and each component of the knee adduction moment. The shaded areas indicate the 95% confidence interval bands for each set of relationships.

Figure 3. Scatterplots of the relationship between minimum frontal plane rearfoot angle and the two components of the knee adduction moment where frontal plane knee angle was found to be an effect modifier (late stance KAM and KAM impulse). Regression lines, 95% confidence interval bands, and the associated r-values are provided for data based on each tertile of the frontal plane knee angle.

Table 1. Summary statistics for entire sample and each contributing sample from the University of British Columbia and Salford University. Data are summarized by the mean [95% confidence interval], except for KL Grade, Bilateral vs. Unilateral involvement, and Sex which are the number of participants in each category.

	All Participants (n=226)		**UBC (n=110)**		**Salford (n=116)**	
Outcome	Mean	95% CI	Mean	95% CI	Mean	95% CI
Age (years)	63.8	[62.6, 65.0]	64.8	[63.3, 66.3]	63.0	[61.2, 64.8]
Height (cm)	167	[166, 168]	165	[163, 167]	169	[167, 171]
Body Mass (kg)	78.8	[76.8, 80.8]	74.0	[71.6, 76.4]	83.3	[80.5, 86.1]
KL Grade n (%)						
2	96 (43%)		57 (52%)		39 (34%)	
3	116 (51%)		47 (43%)		69 (59%)	
4	14 (6.2%)		6 (5%)		8 (7%)	
Bilateral:Unilateral[†] (n)	114:112		85:25			29:87
Sex (n Males : n Females)	100:126		29:81		71:45	
WOMAC Pain subscale (0-20)	9.0	[8.54, 9.54]	6.4	[5.8, 7.0]	11.4	[10.9, 11.9]
Velocity (m/s)	1.14	[1.12, 1.17]	1.19	[1.16, 1.22]	1.10	[1.07, 1.14]
Early stance KAM (Nm/kg)	0.436	[0.415, 0.457]	0.453	[0.423, 0.483]	0.42	[0.391, 0.449]
KAM at 50% of stance (Nm/kg*s)	0.287	[0.268, 0.306]	0.264	[0.239, 0.289]	0.308	[0.280, 0.336]
Late stance KAM (Nm/kg)	0.364	[0.343, 0.385]	0.334	[0.305, 0.363]	0.394	[0.364, 0.424]
KAM impulse (Nm/kg*s)	0.177	[0.166, 0.188]	0.162	[0.148, 0.176]	0.191	[0.175, 0.208]
Frontal plane rearfoot angle at initial contact (°)	2.3	[1.8, 2.8]	2.9	[2.2, 3.6]	1.7	[1.0, 2.5]
Minimum frontal plane rearfoot angle (°)	-4.3	[-4.7, -3.9]	-3.2	[-3.8, -2.6]	-5.4	[-6.0, -4.8]
Frontal plane rearfoot angle excursion (°)	9.0	[8.4, 9.5]	7.8	[7.2, 8.3]	10.1	[9.2, 11.0]
Static frontal plane rearfoot angle (°)	-2.0	[-2.6, -1.5]	-3.6	[-4.4, -2.7]	-0.6	[-1.1, -0.0]
Frontal plane knee angle during midstance (°)	-1.5	[-2.1, -0.8]	-1.0	[-2.0, 0.0]	-1.9	[-2.8, -1.1]

Abbreviations: KL Grade, Kellgren and Lawrence Grade; OA, osteoarthritis; WOMAC, Wester Ontario and McMaster Osteoarthritis Index; KAM, Knee Adduction Moment; 95% CI, 95% confidence interval. [†]Note that both radiographic findings and presence of pain was required to characterize osteoarthritis in a given knee.

Table 2. Mediation analysis results for the relationship between minimum frontal plane rearfoot angle and the four KAM outcomes, mediated by the frontal plane knee angle. Every model showed complete mediation of the relationship.

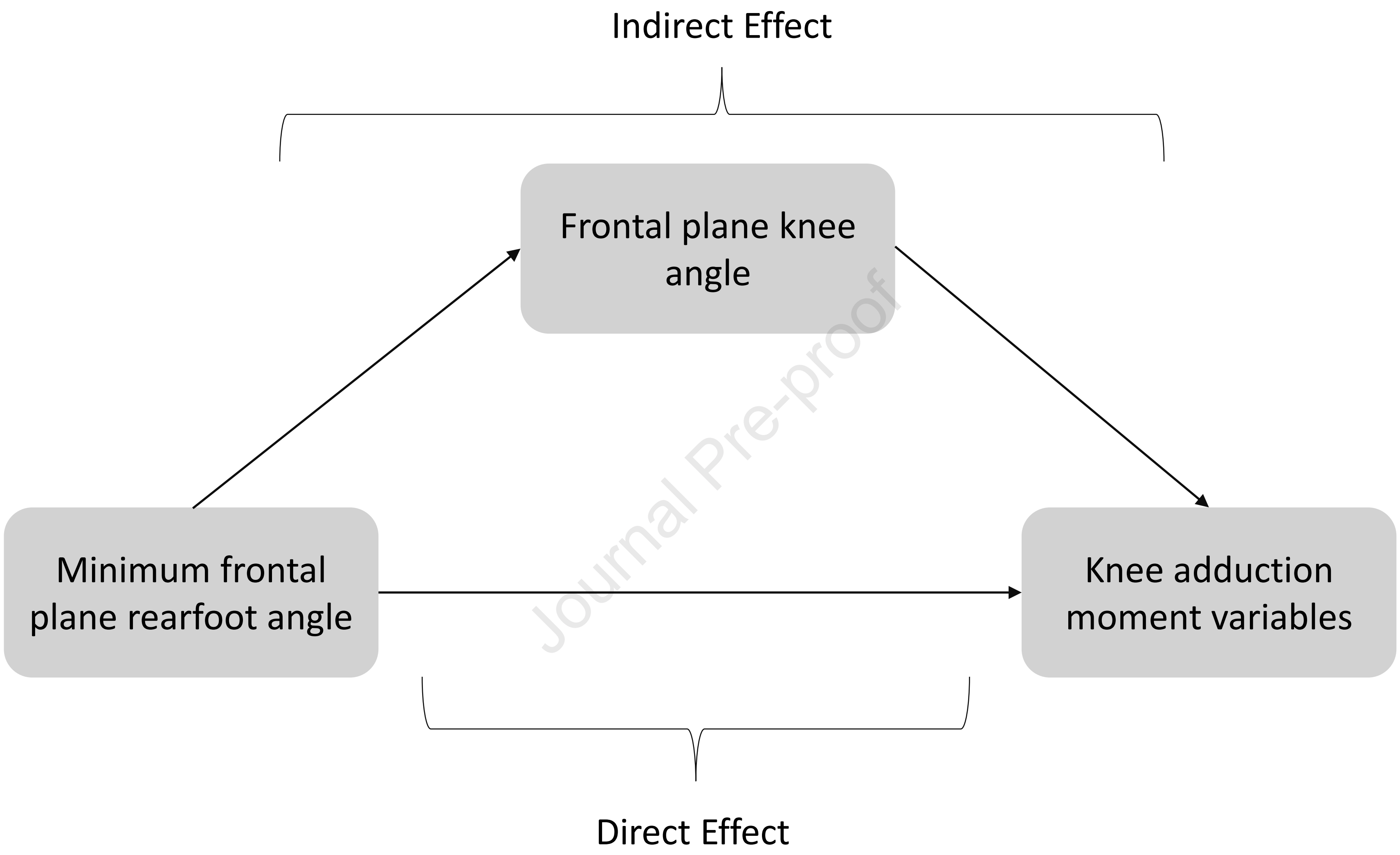
	Total Effect		Direct Effect		Indirect Effect	
	Effect [95% CI]	p	Effect [95% CI]	p	Effect [95% CI]	p
Early Stance KAM	-0.021 [-0.027, -0.015]	< .001	-0.001 [-0.006, -0.003]	0.521	-0.020 [-0.024, -0.015]	< .001
KAM at 50% Stance	-0.019 [-0.024, -0.014]	< .001	-0.003 [-0.007, -0.002]	0.195	-0.016 [-0.020, -0.012]	< .001
Late Stance KAM	-0.020 [0.003, -0.014]	< .001	-0.001 [-0.006, 0.004]	0.631	-0.019 [-0.024, -0.014]	< .001
KAM Impulse	-0.011 [-0.014, -0.008]	< .001	-0.001 [-0.003, 0.001]	0.403	-0.010 [-0.013, -0.008]	< .001

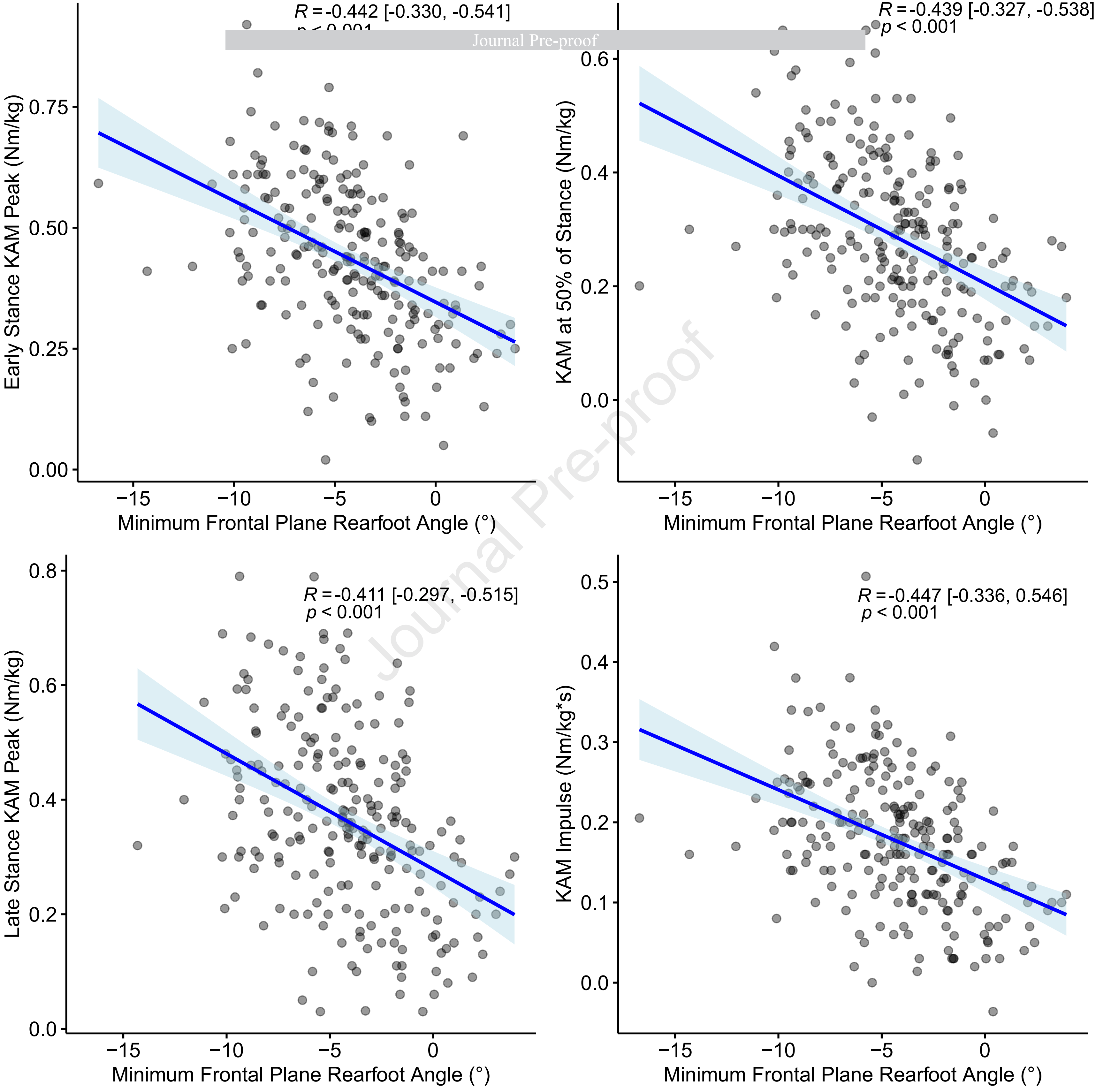
* Abbreviations: 95% CI, 95% confidence interval; KAM, knee adduction moment.

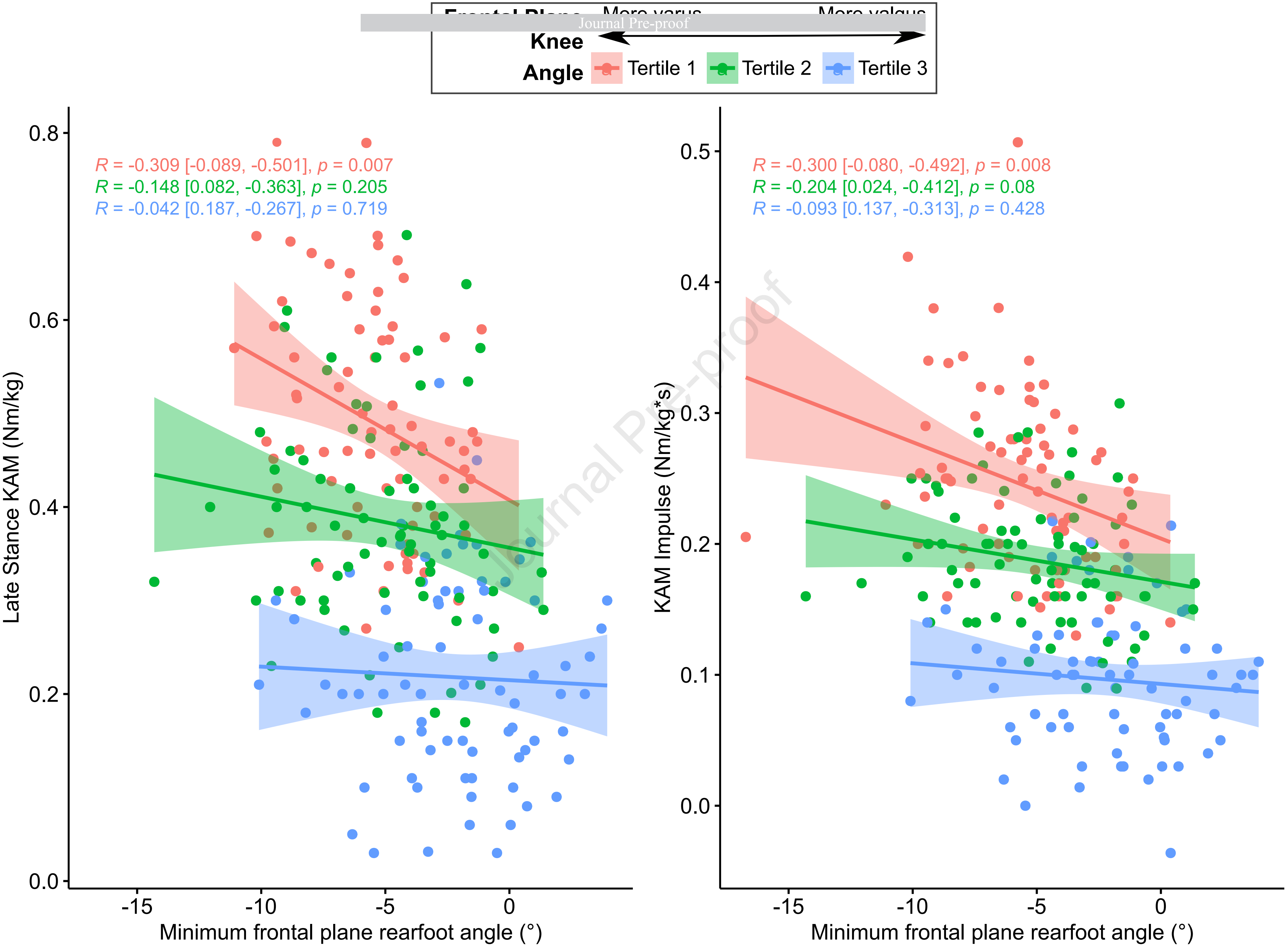
Table 3. Multivariable regression results for relationship between minimum frontal plane rearfoot angle and the four knee adduction moment outcomes. Each model builds on the previous, where Model 1 included the minimum frontal plane rearfoot angle and a binary variable for the two data sets (UBC and Salford). Model 2 added the covariates gait velocity and height, which were only carried forward only if they significantly improved the model. Note that Model 3 (confounding) was not created for the frontal plane knee angle as it was considered a mediator. Model 4 included the interaction of minimum frontal plane rearfoot angle and frontal plane knee adduction angle. Grey areas indicate that the particular variable had not yet entered the modelling progression.

	Model 1: Preliminary Models			**Model 2: Covariate Models**			**Model 4: Effect Modification Models**		
	β [95%CI]	p	R^2 (adj R^2)	β [95%CI]	p	R^2 (adj R^2)	β [95%CI]	p	R^2 (adj R^2)
Early Stance KAM									
Minimum frontal plane rearfoot angle	-0.025 [-0.031, -0.019]	< .001	0.262 (0.256)	-0.025 [-0.031, -0.020]	< .001	0.272 (0.259)	-0.005 [-0.009, 0.000]	0.042	0.684 (0.679)
Site (indicator)	0.088 [0.049, 0.126]	< .001		0.097 [0.057, 0.137]	< .001		0.067 [0.042, 0.092]	< .001	
Gait velocity				-0.018 [-0.118, 0.082]	0.721		-		
Height				0.002 [-0.000, 0.003]	0.086		-		
Frontal plane knee angle							-0.022 [-0.026, -0.018]	< .001	
Interaction term							0.001 [-0.001, 0.001]	0.076	
KAM at 50% of Stance									
Minimum frontal plane rearfoot angle	-0.019 [-0.024, -0.013]	<.001	0.192 (0.185)	-0.018 [-0.024, -0.013]	< .001	0.280 (0.267)	-0.002 [-0.007, 0.003]	0.380	0.590 (0.579)
Site (indicator)	-0.003 [-0.040, 0.033]	0.866		0.024 [-0.013, 0.060]	0.198		-0.005 [0.033, 0.023]	0.704	
Gait velocity				-0.224 [-0.314, -0.133]	< .001		-0.143 [-0.213, -0.073]	< .001	
Height				-0.002 [-0.001, 0.004]	0.013		0.001 [-0.001, 0.002]	0.293	
Frontal plane knee angle							-0.018 [-0.023, -0.014]	< .001	
Interaction term							0.000 [-0.000, 0.001]	0.360	
Late Stance KAM									
Minimum frontal plane rearfoot angle	-0.019 [-0.025, -0.013]	< .001	0.173 (0.165)	-0.019 [-0.025, -0.013]	< .001	0.191 (0.177)	0.002 [-0.004, 0.007]	0.562	0.598 (0.590)
Site (indicator)	-0.020 [-0.061, 0.020]	0.328		-0.005 [-0.048, 0.037]	0.803		-0.041 [-0.070, -0.013]	0.005	
Gait velocity				-0.090 [-0.197, 0.016]	0.095		-		
Height				0.002 [0.000, 0.004]	0.089		-		
Frontal plane knee angle							-0.021 [-0.025, -0.016]	< .001	
Interaction term							0.001 [0.000, 0.002]	0.021	
KAM Impulse									
Minimum frontal plane rearfoot angle	-0.011 [-0.014, -0.008]	< .001	0.201 (0.193)	-0.011 [-0.014, -0.008]	< .001	0.310 (0.298)	-0.000 [-0.003, 0.002]	0.844	0.687 (0.679)
Site (indicator)	-0.005 [-0.026, 0.016]	0.648		0.013 [-0.007, 0.034]	0.207		-0.006 [-0.020, 0.009]	0.445	
Gait velocity				-0.140 [-0.192, -0.089]	< .001		-0.089 [-0.124, -0.054]	< .001	
Height				0.002 [0.001, 0.003]	0.001		0.001 [0.000, 0.001]	0.039	
Frontal plane knee angle							-0.011 [-0.013, -0.009]	< .001	
Interaction term							0.000 [0.000, 0.001]	0.045	

Abbreviations: KAM, knee adduction moment; 95% CI, 95% confidence interval; adj R^2, adjusted R^2.


Indirect Effect
Frontal plane knee angle
Minimum frontal plane rearfoot angle
Knee adduction moment variables
Direct Effect


R = -0.442 [-0.330, -0.541]
p < 0.001
Early Stance KAM Peak (Nm/kg)
0.00
0.25
0.50
0.75
−15
−10
−5
0
Minimum Frontal Plane Rearfoot Angle (°)
R = -0.439 [-0.327, -0.538]
p < 0.001
KAM at 50% of Stance (Nm/kg)
0.0
0.2
0.4
0.6
−15
−10
−5
0
Minimum Frontal Plane Rearfoot Angle (°)
R = -0.411 [-0.297, -0.515]
p < 0.001
Late Stance KAM Peak (Nm/kg)
0.0
0.2
0.4
0.6
0.8
−15
−10
−5
0
Minimum Frontal Plane Rearfoot Angle (°)
R = -0.447 [-0.336, 0.546]
p < 0.001
KAM Impulse (Nm/kg*s)
0.0
0.1
0.2
0.3
0.4
0.5
−15
−10
−5
0
Minimum Frontal Plane Rearfoot Angle (°)


Frontal Plane Knee Angle
More varus
More valgus
Tertile 1
Tertile 2
Tertile 3
R = -0.309 [-0.089, -0.501], p = 0.007
R = -0.148 [0.082, -0.363], p = 0.205
R = -0.042 [0.187, -0.267], p = 0.719
Late Stance KAM (Nm/kg)
0.0
0.2
0.4
0.6
0.8
-15
-10
-5
0
Minimum frontal plane rearfoot angle (°)
R = -0.300 [-0.080, -0.492], p = 0.008
R = -0.204 [0.024, -0.412], p = 0.08
R = -0.093 [0.137, -0.313], p = 0.428
KAM Impulse (Nm/kg*s)
0.0
0.1
0.2
0.3
0.4
0.5
-15
-10
-5
0
Minimum frontal plane rearfoot angle (°)