

Medial knee joint contact force in the intact limb during walking in recently ambulatory service members with unilateral limb loss: cross-sectional study

Ross H Miller^{Corresp., 1,2}, Rebecca L Krupenevich¹, Alison L Pruziner^{1,3,4}, Erik J Wolf^{3,4}, Barri L Schnall³

¹ Department of Kinesiology, University of Maryland, College Park, Maryland, United States

² Neuroscience & Cognitive Science Program, University of Maryland, College Park, Maryland, United States

³ Walter Reed National Military Medical Center, Bethesda, Maryland, United States

⁴ DoD-VA Extremity Trauma and Amputation Center of Excellence, United States

Corresponding Author: Ross H Miller

Email address: rosshm@umd.edu

Background: Individuals with unilateral lower limb amputation have a high risk of developing knee osteoarthritis (OA) in their intact limb as they age. This risk may be related to joint loading experienced earlier in life. We hypothesized that loading during walking would be greater in the intact limb of young US military Service Members with limb loss than in controls with no limb loss.

Methods: cross-sectional instrumented gait analysis at self-selected walking speeds with a limb loss group (N=10, age 27 ± 5 years, 170 ± 36 days since last surgery) including five service members with transtibial limb loss and five with transfemoral limb loss, all walking independently with their first prosthesis for approximately two months. Controls (N=10, age 30 ± 4 years) were service members with no overt demographical risk factors for knee OA. 3D inverse dynamics modeling was performed to calculate joint moments and medial knee joint contact forces (JCF) were calculated using a reduction-based musculoskeletal modeling method and expressed relative to body weight (BW).

Results: Peak JCF and maximum JCF loading rate were significantly greater in limb loss (184% BW, 2469% BW/s) vs. controls (157% BW, 1985% BW/s), with large effect sizes. Results were robust to probabilistic perturbations to the knee model parameters.

Discussion: Assuming these data are reflective of joint loading experienced in daily life, they support a “mechanical overloading” hypothesis for the risk of developing knee OA in the intact limb of limb loss subjects. Examination of the evolution of gait mechanics, joint loading, and joint health over time, as well as interventions to reduce load or strengthen the ability of the joint to withstand loads, is warranted.

1 Title:

2 Medial knee joint contact force in the intact limb during walking in recently ambulatory service
3 members with unilateral limb loss: cross-sectional study

4

5 Authors:

6 Ross H. Miller^{1,2} (corresponding author)

7 Rebecca L. Krupenevich¹

8 Alison L. Pruziner^{1,3,4}

9 Erik J. Wolf^{3,4}

10 Barri L. Schnall⁴

11

12 ¹Department of Kinesiology, University of Maryland, College Park, MD, USA

13 ²Neuroscience & Cognitive Science Program, University of Maryland, College Park, MD, USA

14 ³DoD-VA Extremity Trauma and Amputation Center of Excellence

15 ⁴Walter Reed National Military Medical Center, Bethesda, MD, USA

16

17 Corresponding author:

18 Ross H. Miller, rosshm@umd.edu

19 **ABSTRACT**

20 **Background:** Individuals with unilateral lower limb amputation have a high risk of developing
21 knee osteoarthritis (OA) in their intact limb as they age. This risk may be related to joint loading
22 experienced earlier in life. We hypothesized that loading during walking would be greater in the
23 intact limb of young US military Service Members with limb loss than in controls with no limb
24 loss.

25
26 **Methods:** cross-sectional instrumented gait analysis at self-selected walking speeds with a limb
27 loss group (N=10, age 27±5 years, 170±36 days since last surgery) including five service
28 members with transtibial limb loss and five with transfemoral limb loss, all walking
29 independently with their first prosthesis for approximately two months. Controls (N=10, age
30 30±4 years) were service members with no overt demographical risk factors for knee OA. 3D
31 inverse dynamics modeling was performed to calculate joint moments and medial knee joint
32 contact forces (JCF) were calculated using a reduction-based musculoskeletal modeling method
33 and expressed relative to body weight (BW).

34
35 **Results:** Peak JCF and maximum JCF loading rate were significantly greater in limb loss (184 %
36 BW, 2469 %BW/s) vs. controls (157 %BW, 1985 %BW/s), with large effect sizes. Results were
37 robust to probabilistic perturbations to the knee model parameters.

38
39 **Discussion:** Assuming these data are reflective of joint loading experienced in daily life, they
40 support a “mechanical overloading” hypothesis for the risk of developing knee OA in the intact
41 limb of limb loss subjects. Examination of the evolution of gait mechanics, joint loading, and
42 joint health over time, as well as interventions to reduce load or strengthen the ability of the joint
43 to withstand loads, is warranted.

44 INTRODUCTION

45 Since 2001, over 1,600 United States military service members have sustained traumatic
46 injuries involving major limb loss (Fischer, 2015). Individuals with unilateral lower limb loss
47 have a high risk of developing secondary physical conditions later in life, including osteoarthritis
48 (OA) in their intact limb (Gailey et al., 2008; Morgenroth et al., 2012). In veterans with
49 unilateral limb loss, the prevalence of knee OA is 30-90% greater in the intact limb compared to
50 veterans without limb loss (Hungerford & Cockin, 1975; Lemaire & Fisher, 1994; Norvell et al.,
51 2005). Most of the subjects in these previous studies were older adults who had been living with
52 their amputations for several decades. Recent reviews have indicated a rising incidence of
53 idiopathic knee OA in the young military population (Showery et al., 2016) and in service
54 members with limb loss specifically (Farrokhi et al., 2016). The younger service members with
55 limb loss from recent conflicts may therefore live with a relatively high risk of developing knee
56 OA for many years.

57 Our long-term goal is to develop interventions that can be implemented early after limb
58 loss to minimize the risk of developing knee OA later in life. Achieving this goal is challenging
59 because the causal mechanisms of OA are unknown. However, mechanical loading is suspected
60 to play a major role in the disease's etiology (Andriacchi & Mündermann, 2006; Maly, 2008;
61 Felson, 2013), and overloading the intact limb by deliberately or subconsciously favoring it
62 during activities of daily living is a long-standing hypothesis for explaining the prevalence of
63 knee OA in the limb loss population (Borgmann, 1960). The fatigue life of human articular
64 cartilage *in vitro* suggests that the stresses from repetitive loading in walking could produce
65 mechanical failure of the superficial collagen fibers well within the human lifespan (Weightman
66 et al., 1978; Bellucci & Seedhom, 2001). Relatedly, the "cartilage conditioning" hypothesis

67 argues that cartilage *in vivo* adapts to withstand frequently encountered stress levels (Seedhom,
68 2006). If abrupt changes in gait mechanics due to amputation and prosthesis use result in sudden
69 increases in loading of the intact limb, these loads could overwhelm the adaptive response of
70 cartilage, particularly if it has recently been weakened due to a long period of unloading from
71 injury, surgery, and recovery. For example, knee cartilage glycosaminoglycan content, which
72 affects the compressive stiffness of cartilage, remains below baseline for at least a year following
73 six weeks of immobilization in humans (Owman et al., 2014). Similar results are seen in animal
74 models (Jurvelin et al., 1986). The time when unilateral limb loss patients first begin walking
75 again could therefore be a particularly important time to assess their joint loading.

76 In this study, we therefore examined knee joint loading in the intact limb of relatively
77 young service members with unilateral limb loss who had recently begun walking independently
78 with their prostheses for the first time. We tested the hypothesis that loading of the medial knee
79 joint, as indicated by the peak, loading rate, and impulse of the medial joint contact force, is
80 greater during self-paced walking in the intact limb of young service members with limb loss
81 than in a control group of similar age and background (young service members) without limb
82 loss. These three outcome variables were chosen because they have all previously been
83 associated with knee OA risk, and it is unknown which is most important. The medial knee was
84 chosen because the knee is the most common site of OA (Centers for Disease Control and
85 Prevention, 2015), and because medial knee OA is more common than lateral knee OA (Wise et
86 al., 2012). An elevated risk of general knee OA has been reported in young military service
87 members with limb loss (Farrokhi et al., 2016). The risk of medial knee OA specifically in this
88 population is unknown, but bone mineral density and joint structure suggest a high risk for
89 medial knee OA in this population (Royer & Koenig, 2005; Morgenroth et al., 2014).

90 Recent studies suggest that the peak external knee adduction moment (KAM), the most
91 widely-used metric for quantifying medial knee joint loading in gait (Foroughi et al., 2009; Simic
92 et al., 2011), is similar in the intact limb of young service members with limb loss vs. controls
93 (Pruziner et al., 2014; Esposito & Wilken, 2014), and that including the external knee flexion
94 moment (KFM) more accurately estimates medial joint loading than using the KAM alone
95 (Manal et al., 2015). We therefore elected to quantify medial knee joint loading using a model
96 that considers the KAM and the KFM as well as the timing of muscle activity within the gait
97 cycle that contributes to these moments (Schipplein & Andriacchi, 1991).

98

99 **MATERIALS & METHODS**

100 *Subjects*

101 The study design was cross-sectional, with a “limb loss” group and a “control” group.
102 The limb loss group consisted of 10 service members with unilateral limb loss. Five subjects had
103 transtibial amputations and five had transfemoral amputations. The descriptive statistics of the
104 limb loss group (mean±SD) were: age 27±5 years, height 1.77±0.05 m, mass 81.1±18.4 kg, and
105 170(36) days from their most recent amputation-related surgery. All subjects were male and had
106 been walking independently without assistive devices other than their prosthesis for an average
107 of two months at the time of data collection. Additional inclusion criteria were no previous
108 diagnosis of OA, no pain during activities of daily living greater than 4 on a 10-point scale, no
109 limb loss elsewhere on the body, no history of traumatic injury to the intact limb, and no history
110 of traumatic brain injury or other medical issues known to affect gait.

111 The control group consisted of 10 male service members with no limb loss and similar
112 descriptive statistics to the limb loss group (age 30±4 years, height 1.79±0.07 m, mass 83.8±14.3

113 kg), who also met all the inclusion criteria. Walter Reed National Military Medical Center
114 granted ethical approval to carry out the study within its facilities (IRB reference number
115 350985). All protocols were approved by the ethics committee. All subjects were briefed on the
116 study protocols and gave informed written consent prior to participating.

117

118 *Experimental Setup*

119 An instrumented gait analysis was performed while subjects walked across a level 15-m
120 walkway. Subjects wore shorts and their own athletic footwear. The limb loss subjects used
121 their own clinically prescribed passive prosthesis. Positions of retroreflective markers on the
122 pelvis and lower limbs were sampled at 120 Hz using 23 optical motion capture cameras (Vicon,
123 Oxford, UK). Ground reaction forces (GRF) were sampled synchronously at 1200 Hz using six
124 force platforms (AMTI, Watertown, MA, USA) embedded in the walkway.

125

126 *Protocol*

127 Subjects walked along the walkway at self-selected speed and cadence. Instructions were
128 to walk in a “normal and comfortable” fashion. Each subject walked back and forth along the
129 walkway until five acceptable trials were collected, with “acceptable” defined as each foot
130 contained entirely within the bounds of a single force platform and both feet never
131 simultaneously contacting the same platform.

132

133 *Data Processing*

134 Marker positions and GRF from each trial were exported to Visual3D (C-Motion,
135 Germantown, MD, USA) for further analysis. Marker positions and GRF were smoothed using a

136 4th-order dual-pass Butterworth filter with cutoff frequencies of 6 Hz and 50 Hz, respectively. A
137 linked-segment model of each subject's pelvis and intact limb was defined using marker
138 positions from a standing calibration trial. The hip joint center was estimated from the positions
139 of the pelvis markers (Bell et al., 1989). The knee center was estimated as the midpoint of the
140 femoral condyle markers, and the ankle joint center was estimated as the midpoint of the malleoli
141 markers. The long axes of the thigh and shank were defined between the proximal and distal
142 joint centers. The frontal plane axis for both segments was defined from the cross-product of the
143 long axis and the vector between the femoral condyles. The sagittal plane axis was the cross-
144 product of the frontal plane and long axes. Segment tracking during gait trials was calculated
145 from the positions of marker clusters on rigid shells.

146 Joint angles during gait were calculated using 6DOF pose estimation, with a Cardan XYZ
147 rotation sequence (Wu & Cavanagh, 1995). Resultant joint forces and moments were calculated
148 by iterative Newton-Euler inverse dynamics beginning at the foot (Selbie et al., 2014). The
149 resultant knee forces and moments were expressed in the shank reference frame.

150

151 ***Joint Contact Force Modeling***

152 Medial knee joint contact forces were calculated using the model of Schipplein and
153 Andriacchi (1991). Muscle moment arms and orientations were defined as quadratic functions of
154 the knee flexion angle using average values for men from Wretenberg et al. (1996). The KFM
155 was assumed to be produced by the quadriceps if the moment was extensor, by the hamstrings if
156 the moment was flexor in swing or during early stance, and by the gastrocnemius if the moment
157 was flexor in late stance. Forces in the individual hamstrings muscles (biceps femoris,
158 semimembranosus, semitendinosus) and the two gastrocnemius heads were distributed by the

159 ratios of their physiological cross-sectional areas from Arnold et al. (2010). The medial contact
160 force was then calculated by balancing the frontal plane moments about the lateral contact point
161 (Fig. 1). Cruciate and collateral ligament forces were included in the contact force calculation
162 using the method described by Morrison (1968). The distance between the medial and lateral
163 tibiofemoral contact points in the frontal plane was assumed to be 5.0 cm on average and was
164 scaled linearly for each subject by the distance between the medial and lateral femoral condyle
165 markers during the standing calibration trial. Baseline model parameters are summarized in
166 Table 1.

167 Note that this model assumes zero antagonistic co-contraction. This assumption could
168 potentially underestimate contact forces around heel-strike, when the quadriceps and hamstrings
169 are both active (Sutherland, 2001). However, since knee muscle co-contraction in early stance is
170 similar between limb loss subjects and controls (Seyedali et al., 2012), this assumption does not
171 bias the results in favor of the hypothesis.

172

173 *Statistical Analysis*

174 The planned comparisons were the peak, loading rate, and impulse of the contact force
175 between groups. These outcome variables were scaled by bodyweight (BW), with the mass of
176 the prosthesis included in this calculation for the limb loss subjects. Loading rate was defined as
177 the maximum loading rate during 10-90% of the time from heel-strike until the first peak.

178 Results will be presented for the transtibial and transfemoral subjects separately.
179 However, due to the small sample sizes, these subjects were combined into a single limb loss
180 group for statistical comparison with the control group. It will be seen that the differences in
181 contact forces between the limb loss and control groups were not driven by the transtibial or

182 transfemoral subjects specifically (i.e. contact forces were similar on average for transtibial and
183 transfemoral subjects).

184 Normality of the outcome variables was assessed using Kolmogorov-Smirnov tests. All
185 tests passed at the $\alpha = 0.05$ level. Subsequently, comparisons between groups were made using
186 independent Student's t -tests ($\alpha = 0.05$, $\beta = 0.20$) with a False Discover Rate adjustment for the
187 multiple outcome variables. The tests were one-tailed due to the directional nature of the
188 hypothesis. 95% confidence intervals (CI) were also calculated. As an additional conservative
189 check due to the small sample sizes, differences were reported only if the effect size was large
190 (Cohen's $d > 0.80$). Effect sizes for between-subjects differences in external knee adduction
191 moment (a common surrogate for medial joint loading) and knee OA initiation and progression
192 are typically much smaller than 0.8 (e.g. Amin et al., 2004; Miyazaki et al., 2002), so the
193 requirement of a large effect size is likely a fairly conservative check.

194

195 ***Sensitivity Analysis***

196 The knee model (Fig. 1) required input parameters for muscle moment arms, orientations,
197 and physiological cross-sectional areas, and the distance between the tibiofemoral contact points.
198 The necessary imaging data to define these parameters on a subject-specific basis were not
199 available, and the same generic parameter values were used for all subjects except for the contact
200 point distance. In such situations, probabilistic approaches are useful for assessing the sensitivity
201 of model output to parameter value uncertainty (Valero-Cuevas et al., 2009). To assess the
202 sensitivity of the contact force results (and the conclusions drawn from them) to these parameter
203 values, standard normal distributions were formed for each parameter with the nominal value as
204 the mean and a coefficient of variation of 10%, which is a reasonable estimate of the typical

205 variation in these parameters in a homogenous adult male population (Hasson & Caldwell,
206 2012). The contact force variables were then re-calculated for each subject using parameters
207 randomly drawn from these distributions, and the statistical analysis was performed again. This
208 process was repeated iteratively until the fraction of iterations with significantly greater outcome
209 variables in the limb loss group changed by under 1% over 100 further iterations. The output of
210 this analysis was the fraction of perturbed parameter sets for which the outcome variable in
211 question (peak, loading rate, or impulse) was greater in the limb loss group, from which the
212 sensitivity of the outcome variables to the assumed model parameters could be judged.

213

214 RESULTS

215 The self-selected walking speeds were similar between groups (1.25 ± 0.19 m/s for limb
216 loss, 1.31 ± 0.10 m/s for controls, $p = 0.40$, $d = 0.39$, $95\%CI = (-0.19, 0.07)$ m/s). Stride durations
217 were also similar between groups (1.16 ± 0.07 s for limb loss, 1.12 ± 0.07 s for controls, $p = 0.24$, d
218 $= 0.55$, $95\%CI = (-0.02, 0.10)$ s). The average medial knee joint contact force waveforms are
219 shown for the transtibial, transfemoral, and control subjects in Fig. 2. The contact forces showed
220 the typical two-peaked pattern seen in instrumented knee replacement studies of older adults
221 without limb loss (Walter et al., 2010; Kutzner et al., 2013; Meyer et al., 2013). For the control
222 subjects, the peak force occurred in early stance and averaged 1.57 ± 0.26 BW, which is within
223 the range of values reported in these studies (1.25-2.20 BW). With the exception of a lack of
224 quadriceps activity in late swing, which did not affect the contact force outcome variables, the
225 muscle forces predicted by the model for the quadriceps, hamstrings, and gastrocnemius (Fig. 3)
226 were consistent with normative electromyogram timing for these muscles (Sutherland, 2001;
227 Seyedali et al., 2012).

228 The peak contact force was greater in the limb loss group than in the control group
229 (1.84 ± 0.37 vs. 1.57 ± 0.26 BW, $p = 0.037$, $d = 0.85$, 95%CI = (-0.01, 0.55) BW). Maximum
230 loading rate was also greater in the limb loss group (24.7 ± 5.4 vs. 19.9 ± 3.2 BW/s, $p = 0.012$, $d =$
231 1.10 , 95%CI = (1.0, 8.7) BW/s). Impulse had a moderate effect size between groups, but were
232 not significantly greater in the limb loss group (0.72 ± 0.12 BW•s for limb loss, 0.64 ± 0.13 BW•s
233 for controls, $p = 0.084$, $d = 0.64$, 95%CI = (-0.03, 0.19) BW•s). Outcome variables are
234 summarized in Fig. 4. The sensitivity analysis converged after about 3,000 iterations (Fig. 5).
235 The loading rate, peak, and impulse were greater in the limb loss group than in the control group
236 ($p < 0.05$, $d > 0.80$) for 98%, 73%, and 25% of these iterations, respectively.

237 The KAM and KFM were not analyzed statistically due to concerns over multiple
238 comparisons with small sample sizes, and the fact that both variables were considered in the
239 calculation of contact forces, but their mean profiles are presented for completeness in Fig. 6.
240 Limb loss subjects tended to have greater peak KFM and KAM than the control subjects, and the
241 transtibial subjects tended to have greater peak KFM than the transfemoral subjects. The
242 primary mechanism by which the transtibial and transfemoral subjects had similar peak contact
243 forces (Fig. 2) despite greater KFM in the transtibial subjects was greater axial resultant joint
244 force in the transfemoral subjects during early stance (Fig. 6).

245

246 **DISCUSSION**

247 In this study we tested the hypothesis that knee joint loading during walking is greater in
248 the intact limb of US Military service members with unilateral limb loss who are relatively
249 young, recently ambulatory, and otherwise healthy, compared to the limbs of service members
250 with similar demographics and no limb loss. Based on the nominal contact force results (Fig. 4)

251 and the probabilistic analysis of model parameters (Fig. 5), we accept this hypothesis with a high
252 degree of confidence based on the loading rate of the medial joint contact force, and with a
253 moderate degree of confidence based on the peak of the medial joint contact force. Impulse of
254 the contact force did not appear to be greater in the limb loss group.

255 Before discussing the implications of these results, we first comment on some limitations.
256 The study included small sample sizes, with a mix of transtibial and transfemoral subjects (five
257 each) in the limb loss group. However, the transtibial and transfemoral subjects had similar
258 average height, mass, and self-selected walking speeds (differences of 0.4 cm, 2.8 kg, and 0.02
259 m/s, respectively), and it can be seen from Fig. 4 that they also had similar contact force results,
260 suggesting that combining these sub-groups into one group was reasonable for the purposes of
261 this study. The limb loss population is difficult to study in large numbers, and we were working
262 with a particular subset of this population (young service members and some fairly restrictive
263 additional inclusion criteria). Due to the small sample size, we took a conservative approach to
264 reporting differences between groups even after adjusting for multiple comparisons, with the
265 requirement of a large effect size. The issues of the knee model parameters and antagonistic co-
266 contraction have already been addressed: these modeling issues may affect the numerical values
267 of the results, but would be unlikely to change the conclusions (Fig. 5). The knee contact model
268 itself (Fig. 1) is a Morrison (1968)-type reduction approach. These models are on the lower end
269 of complexity among the range of musculoskeletal models used for this purpose, but have a long
270 history in biomechanics (Morrison, 1968; Schipplein & Andriacchi, 1991; DeVita & Hortobágyi,
271 2001; Messier et al., 2011; Willy et al., 2016). History/popularity alone do not validate the
272 approach, but this approach produces similar muscle forces to more mathematically intensive

273 static optimization methods (Kernozek et al., 2016) and knee contact forces in good agreement
274 with instrumented knee replacement measurements (Willy et al., 2016).

275 The time point at which the gait data were obtained from the limb loss group (shortly
276 after they became independently mobile) could be viewed as a limitation since the gait
277 mechanics of these individuals may change in the future. Although the knee kinetics in the
278 present limb loss subjects (Fig. 6) are similar to those in studies on more experienced prosthesis
279 users (Royer & Koenig, 2005; Russell Esposito & Wilken, 2014), the data here may not
280 represent the “typical” or “average” loads these subjects will experience later in life, due for
281 example to motor learning, experience, changes in fitness, or use of different prostheses.
282 However, the focus on joint loading early on in the rehabilitation process can also be viewed as a
283 strength of the present study. Human articular cartilage appears to undergo at least some degree
284 of structural and functional atrophy in the absence of mechanical loading, and it is unclear if
285 these changes are fully reversible (Vanwanseele et al., 2002; Hudelmaeir et al., 2006; Souza et
286 al., 2012; Owman et al., 2014). When new prosthesis users first begin walking independently,
287 their joints have likely undergone a period of at least several weeks with no or minimal
288 mechanical loading following injury, surgery, and recovery. At this early time, we speculate that
289 placing abnormal loads on the intact limb may be particularly dangerous for the future health of
290 the knee. To minimize this risk, we suggest that long periods of unloading should be avoided to
291 the extent that doing so is safe and feasible for the patient.

292 To the knowledge of the authors, the present study is the first to show that medial knee
293 joint contact forces were greater in the intact limb than in controls. A recent forward dynamics
294 simulation study showed a similar result for the total joint contact force during walking in
295 individuals with unilateral transtibial limb loss (Silverman & Neptune, 2014). Knee OA has a

296 rising incidence among young United States military service members over the past 10 years,
297 and there is a need to develop more effective preventive strategies in at-risk sub-groups of this
298 population (Showery et al., 2016). There are presently no longitudinal studies on baseline joint
299 loading and the initiation of knee OA in the limb loss population. However, Morgenroth et al.
300 (2014) found that the KAM peak, impulse, and loading rate were all significantly correlated with
301 the degree of knee structural abnormality present in the intact limb of middle-aged adults (mean
302 age 56 years) with unilateral transfemoral amputations. The present results suggest that
303 relatively high loads are present on the medial knee of the intact limb when young service
304 members with limb loss begin to walk independently, and when interpreted in light of
305 Morgenroth et al. (2014), that the long-term consequence of these loads may be structural
306 degeneration of the knee. These suggestions are in need of verification in longitudinal studies.

307 Relatedly, while the present results suggest medial knee joint loading was greater in the
308 limb loss group, the size of the “minimum meaningful difference” that actually affects the risk
309 for knee OA is unknown. Studies using the external knee adduction moment suggest that effect
310 sizes for differences in medial joint loading during walking and the initiation and progression
311 knee OA in older adults may be small (Amin et al., 2004; Miyazaki et al., 2002), but it is
312 unknown if this suggestion generalized to actual medial joint contact forces or to a younger
313 military limb loss population. Two recent studies suggest that the “minimum detectable change”
314 in medial knee joint loading from gait modification is about 0.25-0.30 BW for peak and about
315 0.04 BW•s for impulse (Gardinier et al., 2013; Barrios & Willson, 2016). Those data were from
316 within-subject designs, where the present data are between-subjects, but they suggest that
317 differences smaller than these values may be difficult to reliably detect in gait analysis, even if
318 they are biologically meaningful. For reference, the average differences between the limb loss

319 and control results in the present study were 0.27 BW for peak and 0.08 BW•s for impulse.
320 Additional knowledge from longitudinal studies is needed to understand which features of joint
321 loading and cartilage mechanics are most important for predicting future structural degeneration,
322 and if critical thresholds for those variables exist.

323 As noted earlier, the KAM is presently the most popular variable for assessing medial
324 knee joint loading in human gait. While we did not analyze the KAM statistically due to
325 concerns over the small sample sizes and multiple comparisons, visual inspection of the KAM
326 (Fig. 6) suggests that similar conclusions would have been reached had we used the KAM rather
327 than the medial joint contact force as the primary outcome variable: greater peak and greater
328 loading rate in the limb loss group. However, we caution that this result was likely coincidental
329 and is not a mechanical requirement. The KAM alone does not dictate the loading of the medial
330 knee, as recent instrumented knee implant studies have shown (Walter et al., 2010; Kutzner et
331 al., 2013; Meyer et al., 2013). Relatedly, the KFM has a major influence on the shape,
332 magnitude, and medial/lateral ratio of joint contact forces, and should be considered when
333 assessing joint loading in gait (Manal et al., 2015).

334

335 CONCLUSIONS

336 In summary, the present results suggest that young, recently ambulatory service members
337 with unilateral limb loss place relatively high loads on their medial knee when walking compared
338 to controls without limb loss. We suggest these loads may be a risk factor for future
339 development of knee OA, a common secondary condition in this population. Further
340 longitudinal study and development of preventive interventions (e.g. physical activity guidelines,
341 prosthesis designs) is warranted. The results also indicate that knee contact model parameter

342 values can be an important consideration in cross-sectional studies. Here we investigated the
343 overall sensitivity (perturbing all contact model parameters simultaneously), but sensitivity to
344 particular parameters of interest may be a relevant topic for future work or specific applications.

345

346 ACKNOWLEDGEMENTS

347 The authors would like to thank Dr. Kurt Manal for helpful suggestions on calculating the
348 knee joint contact forces and Mrs. Jenna Trout for her assistance with data collection and
349 processing.

350

351 REFERENCES

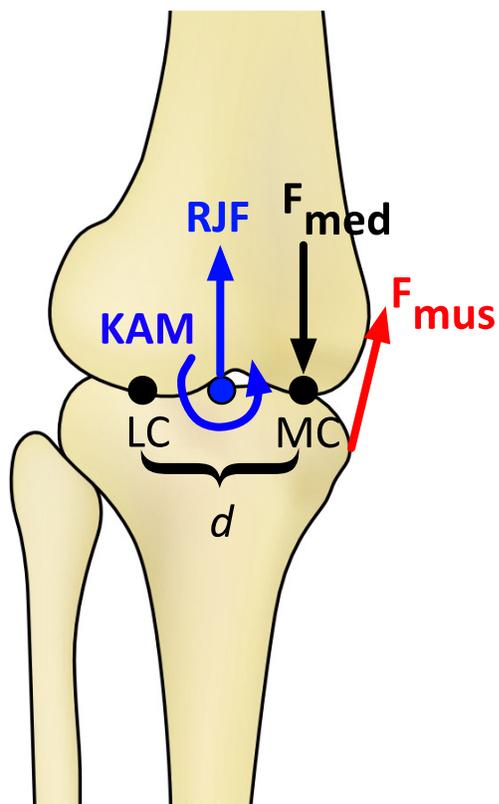
- 352 Amin S, Lueopongsak N, McGibbon CA, LaValley MP, Krebs DE, and Felson DT (2004).
353 Knee adduction moment and development of chronic knee pain in elders. *Arthritis &*
354 *Rheumatism* **51**, 371-376.
- 355
356 Andriacchi TP and Mündermann A (2006). The role of ambulatory mechanics in the initiation
357 and progression of knee osteoarthritis. *Current Opinion in Rheumatology* **18**, 514-518.
- 358
359 Arnold EM, Ward SR, Lieber RL, and Delp SL (2010). A model of the lower limb for analysis
360 of human movement. *Annals of Biomedical Engineering* **38**, 269-279.
- 361
362 Arokoski JPA, Jurvelin JS, Väätäinen U, and Helminen HJ (2000). Normal and pathological
363 adaptations of articular cartilage to joint loading. *Scandinavian Journal of Medicine & Science*
364 *in Sports* **10**, 186-198.
- 365
366 Barrios J and Willson J (2016). Minimum detectable change in medial tibiofemoral contact
367 force parameters: derivation and application to a load-altering intervention. *Journal of Applied*
368 *Biomechanics*, doi: 10.1123/jab.2016-0163.
- 369
370 Bell AL, Brand RA, and Peterson DR (1989). Prediction of hip joint centre location from
371 external landmarks. *Human Movement Science* **8**, 3-16.
- 372
373 Bellucci G and Seedhom BB (2001). Mechanical behaviour of articular cartilage under tensile
374 cyclic load. *Rheumatology* **40**, 1337-1345.
- 375
376 Borgmann F (1960). Zur gutachtlichen beurteilung von rückenbeschwerden und befunden bei
377 Oberschamputation. *Zeitschrift für Orthopädie und ihre Grenzgebiete* **93**, 351-64.
- 378

- 379 Centers for Disease Control and Prevention (2015). Osteoarthritis. Retrieved from:
380 <http://www.cdc.gov/arthritis/basics/osteoarthritis.htm>, June 6, 2016.
381
- 382 DeVita P and Hortobágyi T (2001). Functional knee brace alters predicted knee muscle and joint
383 forces in people with ACL reconstruction during walking. *Journal of Applied Biomechanics* **17**,
384 297-311.
385
- 386 Esposito ER and Wilken JM (2014). Biomechanical risk factors for knee osteoarthritis when
387 using passive and powered ankle-foot prostheses. *Clinical Biomechanics* **29**, 1186-1192.
388
- 389 Farrokhi S, Mazzone B, Yoder A, Grant K, and Wyatt M (2016). A narrative review of the
390 prevalence and risk factors associated with development of knee osteoarthritis after traumatic
391 unilateral lower limb amputation. *Military Medicine* **181**, 38-44.
392
- 393 Felson DT (2013). Osteoarthritis as a disease of mechanics. *Osteoarthritis & Cartilage* **21**, 10-
394 15.
395
- 396 Fischer H (2015). *A Guide to US Military Casualty Statistics: Operation Freedom's Sentinel,*
397 *Operation Inherent Resolve, Operation New Dawn, Operation Iraqi Freedom, and Operation*
398 *Enduring Freedom*. Washington, DC: Congressional Research Service 7-5700.
399
- 400 Foroughi N, Smith R, and Vanwanseele B (2009). The association of external knee adduction
401 moment with biomechanical variables in osteoarthritis: a systematic review. *The Knee* **16**, 303-
402 309.
403
- 404 Gailey R, Allen K, Castles J, Kucharik J, and Roeder M (2008). Review of secondary physical
405 conditions associated with lower-limb amputation and long-term prosthesis use. *Journal of*
406 *Rehabilitation Research & Development* **45**, 15-30.
407
- 408 Gardinier ES, Manal K, Buchanan TS, and Snyder-Mackler L (2013). Minimum detectable
409 change for knee joint contact force estimates using an EMG-driven model. *Gait & Posture* **38**,
410 1051-1053.
411
- 412 Hasson CJ and Caldwell GE (2012). Effects of age on mechanical properties of dorsiflexor and
413 plantarflexor muscles. *Annals of Biomedical Engineering* **40**, 1088-1101.
414
- 415 Hudelmaier M, Glaser C, Hausschild A, Burgkart R, and Eckstein F (2006). Effects of joint
416 loading and reloading on human cartilage morphology and function, muscle cross-sectional
417 areas, and bone density – a quantitative case report. *Journal of Musculoskeletal & Neuronal*
418 *Interactions* **6**, 284-290.
419
- 420 Hungerford D and Cockin J (1975). Fate of the retained lower limb joints in second World War
421 amputees. *Journal of Bone & Joint Surgery* **57**, 111.
422
- 423 Jurvelin J, Kiviranta I, Tammi M, and Helminen HJ (1986). Softening of canine articular
424 cartilage after immobilization of the knee joint. *Clinical Orthopaedics* **201**, 246-252.

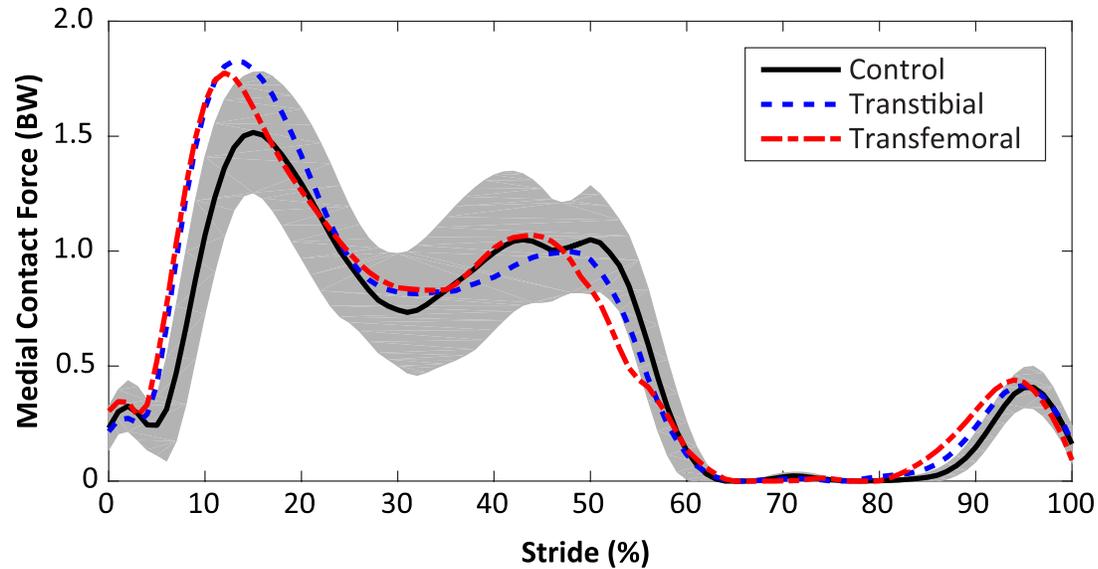
425
426 Kernozek T, Gheidi N, and Ragan R (2016). Comparison of estimates of Achilles tendon
427 loading from inverse dynamics and inverse dynamics-based static optimisation during running.
428 *Journal of Sports Sciences*, doi: 10.1080/02640414.2016.1255769.
429
430 Kutzner I, Trepczynski A, Heller MO, and Bergmann G (2013). Knee adduction moment and
431 medial contact force: facts about their correlation during gait. *PLoS ONE* **8**, e81036.
432
433 Lemaire ED and Fisher FR (1994). Osteoarthritis and elderly amputee gait. *Archives of*
434 *Physical Medicine & Rehabilitation* **75**, 1094-1099.
435
436 Maly MR (2008). Abnormal and cumulative loading in knee osteoarthritis. *Current Opinion in*
437 *Rheumatology* **20**, 547-552.
438
439 Manal K, Gardinier E, Buchanan TS, and Snyder-Mackler L (2015). A more informed
440 evaluation of medial compartment loading: the combined use of the knee adduction and flexor
441 moments. *Osteoarthritis & Cartilage* **23**, 1107-1111.
442
443 Messier SP, Legault C, Loeser RF, Van Arsdale SG, Davis C, Ettinger WH, and DeVita P
444 (2011). Does high weight loss in older adults with knee osteoarthritis affect bone-on-bone joint
445 loads and muscle forces during walking? *Osteoarthritis & Cartilage* **19**, 272-280.
446
447 Meyer AJ, D'Lima DD, Besier TF, Lloyd DG, Colwell CW, and Fregly BJ (2013). Are external
448 knee load and EMG measures accurate indicators of internal knee contact forces during gait?
449 *Journal of Orthopaedic Research* **31**, 921-929.
450
451 Miller RH, Edwards WB, Brandon SCE, Morton AM, and Deluzio KJ (2014). Why don't most
452 runners get knee osteoarthritis? A case for per-unit-distance loads. *Medicine & Science in Sports*
453 *& Exercise* **46**, 572-579.
454
455 Miller RH, Esterson AY, and Shim JK (2015). Joint contact forces when minimizing the
456 external knee adduction moment by gait modification: a computer simulation study. *The Knee*
457 **22**, 481-489.
458
459 Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, and Shimada S (2002). Dynamic load at
460 baseline can predict radiographic disease progression in medial compartment knee osteoarthritis.
461 *Annals of the Rheumatic Diseases* **61**, 617-622.
462
463 Morgenroth DC, Gellhorn AC, and Suri P (2012). Osteoarthritis in the disabled population: a
464 mechanical perspective. *Physical Medicine & Rehabilitation* **4**, S20-S27.
465
466 Morgenroth DC, Medverd JR, Seyedali M, and Czerniecki JM (2014). Relationship between
467 knee joint loading rate during walking and degenerative changes on magnetic resonance
468 imaging. *Clinical Biomechanics* **29**, 664-670.
469

- 470 Morrison JB (1968). Bioengineering analysis of force actions transmitted by the knee joint.
471 *Biomedical Engineering* **3**, 164-170.
472
- 473 Norvell DC, Czerniecki JM, Reiber GE, Maynard C, Pecoraro JA, and Weiss NS (2005). The
474 prevalence of knee pain and symptomatic knee osteoarthritis among veteran traumatic amputees
475 and nonamputees. *Archives of Physical Medicine & Rehabilitation* **86**, 487-493.
476
- 477 Owman H, Tiderius CJ, Ericsson YB, and Dahlberg LE (2014). Long-term effect of removal of
478 knee joint loading on cartilage quality evaluated by delayed gadolinium-enhanced magnetic
479 resonance imaging of cartilage. *Osteoarthritis & Cartilage* **22**, 928-932.
480
- 481 Pruziner AL, Werner KM, Copple TJ, Hendershot BD, and Wolf EJ (2014). Does intact limb
482 loading differ in Servicemembers with traumatic lower limb loss? *Clinical Orthopaedics &
483 Related Research* **472**, 3068-3075.
484
- 485 Royer T and Koenig M (2005). Joint loading and bone mineral density in persons with
486 unilateral, trans-tibial amputation. *Clinical Biomechanics* **20**, 1119-1125.
487
- 488 Schipplein OD and Andriacchi TP (1991). Interaction between active and passive knee
489 stabilizers during level walking. *Journal of Orthopaedic Research* **9**, 113-119.
490
- 491 Seedhom BB (2006). Conditioning of cartilage during normal activities is an important factor in
492 the development of osteoarthritis. *Rheumatology* **45**, 146-149.
493
- 494 Selbie WS, Hamill J, and Kepple T (2014). Three-dimensional kinetics. In: Robertson DGE,
495 Caldwell GE, Hamill J, Kamen G, and Whittlesey SN (eds.), *Research Methods in Biomechanics*
496 2nd Edition (pp. 151-176). Champaign: Human Kinetics.
497
- 498 Seyedali M, Czerniecki JM, Morgenroth DC, and Hahn ME (2012). Co-contraction patterns of
499 trans-tibial ankle and knee musculature during gait. *Journal of NeuroEngineering &
500 Rehabilitation* **9**, 29.
501
- 502 Showery JE, Kusnezov NA, Dunn JC, Bader JO, Belmont PJ, and Waterman BR (2016). The
503 rising incidence of degenerative and posttraumatic osteoarthritis of the knee in the United States
504 military. *Journal of Arthroplasty*, doi: 10.1016/j.arth.2016.03.026.
505
- 506 Silverman AK and Neptune RR (2014). Three-dimensional knee joint contact forces during
507 walking in unilateral transtibial amputees. *Journal of Biomechanics* **47**, 2556-2562.
508
- 509 Simic M Hinman RS, Wrigley TV, Bennell KL, and Hunt MA (2011). Gait modification
510 strategies for altering medial knee joint load: a systematic review. *Arthritis Care & Research* **63**,
511 405-426.
512
- 513 Souza RB, Baum T, Wu S, Feeley BT, Kadel N, Li X, Link TM, and Majumdar S (2012).
514 Effects of unloading on knee articular cartilage T1rho and T2 magnetic resonance imaging
515 relaxation times: a case series. *Journal of Orthopaedic & Sports Physical Therapy* **42**, 511-520.

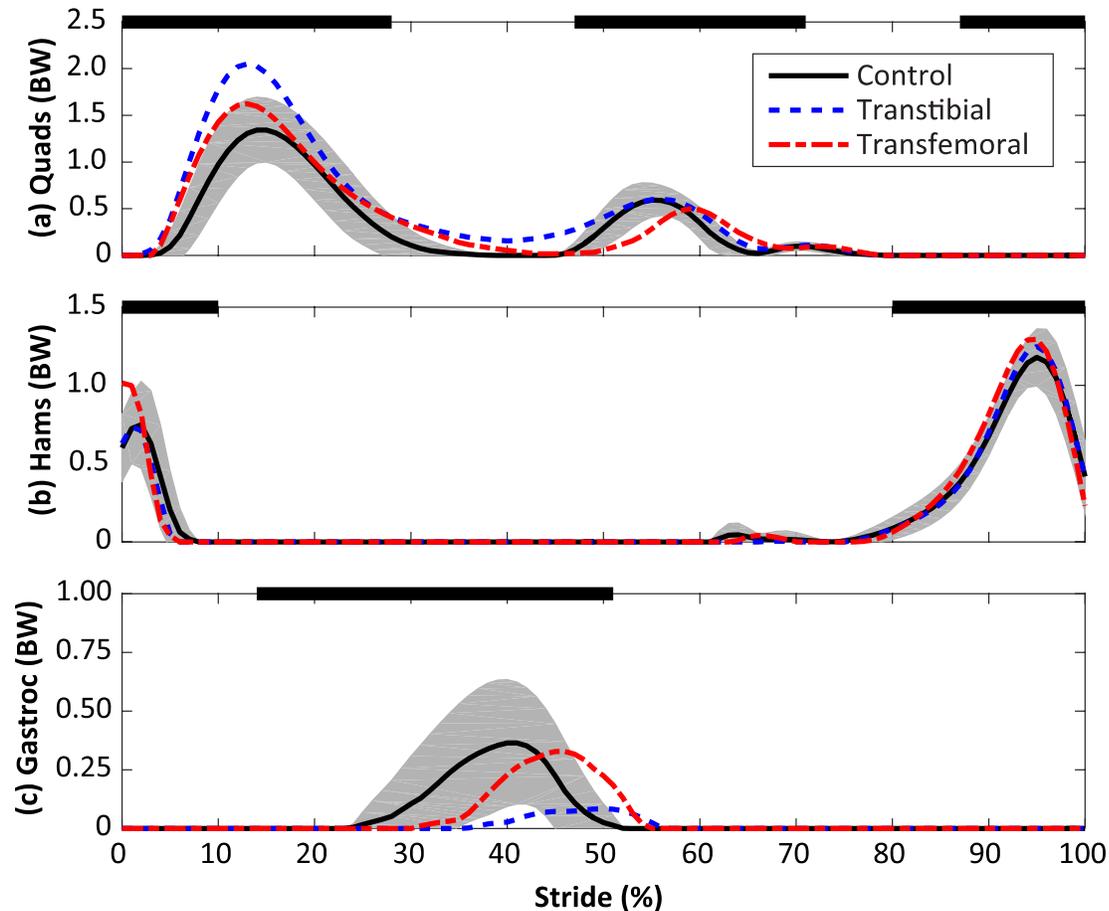
- 516
517 Sutherland DH (2001). The evolution of clinical gait analysis part 1: kinesiological EMG. *Gait*
518 *& Posture* **14**, 61-70.
519
- 520 Terzidis I, Totlis T, Papathanasiou E, Sideridis A, Vlasis K, and Natsis K (2012). Gender and
521 side-to-side differences of femoral condyles morphology: osteometric data from 360 Caucasian
522 dried femori. *Anatomy Research International* **2012**, 679658.
523
- 524 Valero-Cuevas FJ, Hoffmann H, Kurse MU, Kutch JJ, and Theodorou EA (2009).
525 Computational models for neuromuscular function. *IEEE Reviews in Biomedical Engineering* **2**,
526 110-135.
527
- 528 Vanwanseele B, Eckstein F, Knecht H, Stüssi E, and Spaepen A (2002). Knee cartilage of spinal
529 cord-injured patients displays progressive thinning in the absence of normal joint loading and
530 movement. *Arthritis & Rheumatism* **46**, 2073-2078.
531
- 532 Walter JP, D'Lima DD, Colwell CW, and Fregly BJ (2010). Decreased knee adduction moment
533 does not guarantee decreased medial contact force during gait. *Journal of Orthopaedic Research*
534 **28**, 1348-1354.
535
- 536 Weightman B, Chappell DJ, and Jenkins EA (1978). A second study on the tensile fatigue
537 properties of human articular cartilage. *Annals of the Rheumatic Diseases* **37**, 58-63.
538
- 539 Willy RW, Meardon SA, Schmidt A, Blaylock NR, Hadding SA, and Willson JD (2016).
540 Changes in tibiofemoral contact forces during running in response to in-field gait retraining.
541 *Journal of Sports Sciences* **34**, 1602-1611.
542
- 543 Wise BL, Niu J, Yang M, Lane NE, Harvey W, Felson DT, Hietpas J, Nevitt M, Sharma L,
544 Torner J, Lewis CE, and Zhang Y (2012). Patterns of compartment involvement in tibiofemoral
545 osteoarthritis in men and women and in Caucasians and African Americans. *Arthritis Care &*
546 *Research* **64**, 847-852.
547
- 548 Wretenberg P, Németh G, Lamontagne M, and Lundin B (1996). Passive knee muscle moment
549 arms measured in vivo with MRI. *Clinical Biomechanics* **11**, 439-446.
550
- 551 Wu G and Cavanagh PR (1995). ISB recommendations for standardization in the reporting of
552 kinematic data. *Journal of Biomechanics* **28**, 1257-1261.



553
554 **Figure 1.** Schematic of the knee model in the frontal plane for calculating the medial knee joint
555 contact force (F_{med}). KAM = knee adduction moment; RJJ = resultant axial joint force; F_{mus} =
556 muscle force, determined by the knee flexion moment; LC and MC = medial and lateral contact
557 points, separated by distance d . F_{med} is calculated by balancing the moments produced about the
558 point LC (Schipplein & Andriacchi, 1991).

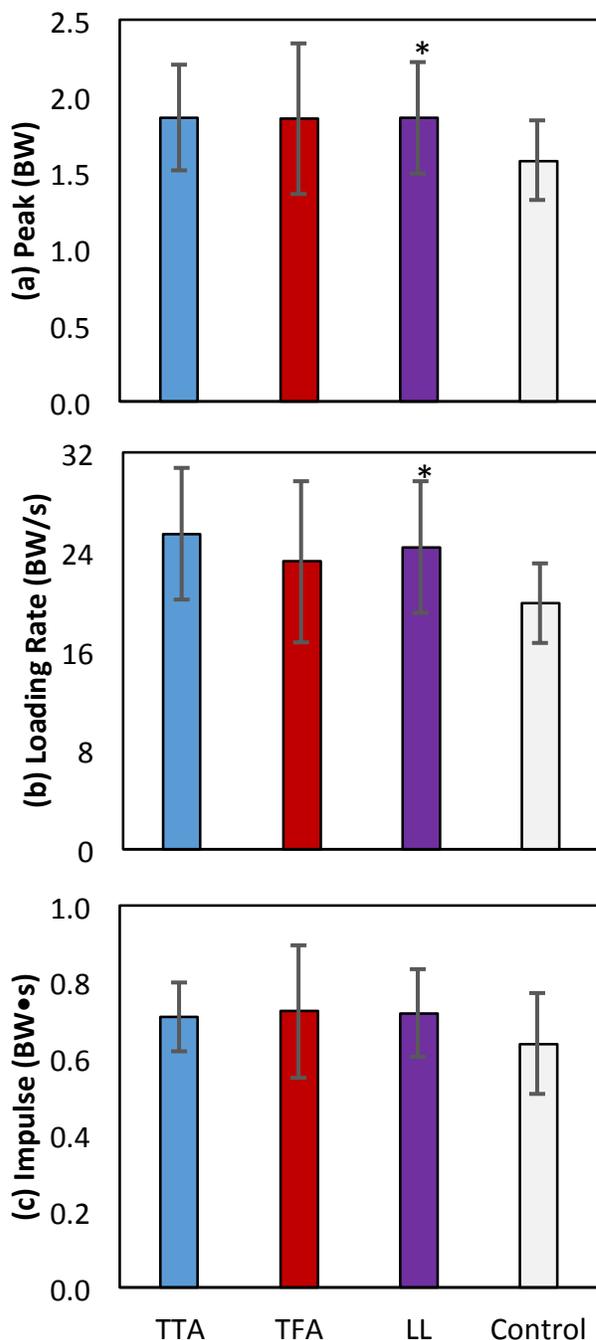


559
560 **Figure 2.** Medial knee joint contact forces in percent bodyweight (BW) during the stride,
561 beginning at heel-strike. Solid, dashed, and dash-dotted lines are means for control, transtibial,
562 and transfemoral subjects. The shaded areas are \pm one between-subjects standard deviation for
563 the control subjects.



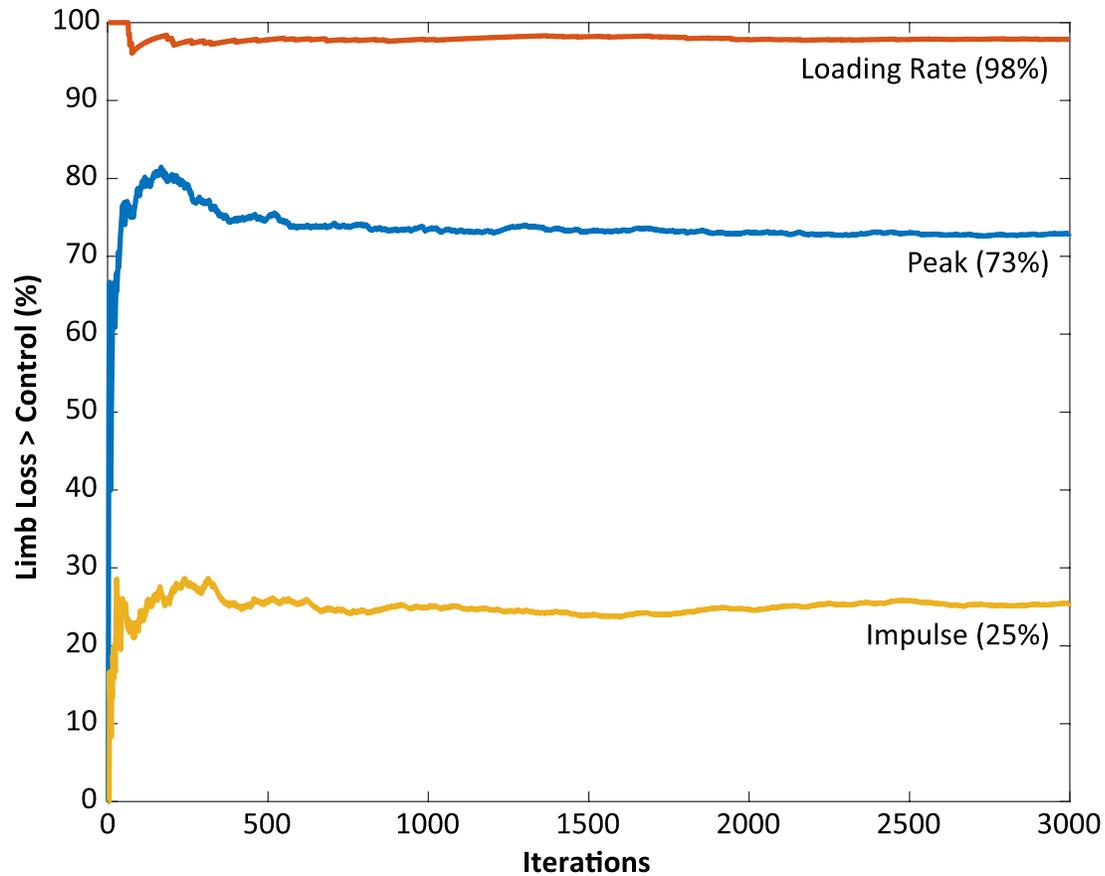
564

565 **Figure 3.** Calculated muscle forces for the quadriceps (Quads, a), hamstrings (Hams, b), and
 566 gastrocnemius (Gastroc, c) muscles during the stride, beginning at heel-strike. Solid, dashed,
 567 and dash-dotted lines are means for control, transtibial, and transfemoral subjects. The shaded
 568 areas are \pm one between-subjects standard deviation for the control subjects. Scaling factors
 569 were bodyweight (BW). The black bars along the top of each panel denote the fraction(s) of the
 570 gait cycle when this muscle group is “on” according to normative electromyograms (Sutherland,
 571 2001), which are similar for the intact limb in limb loss subjects (Seyedali et al., 2012).

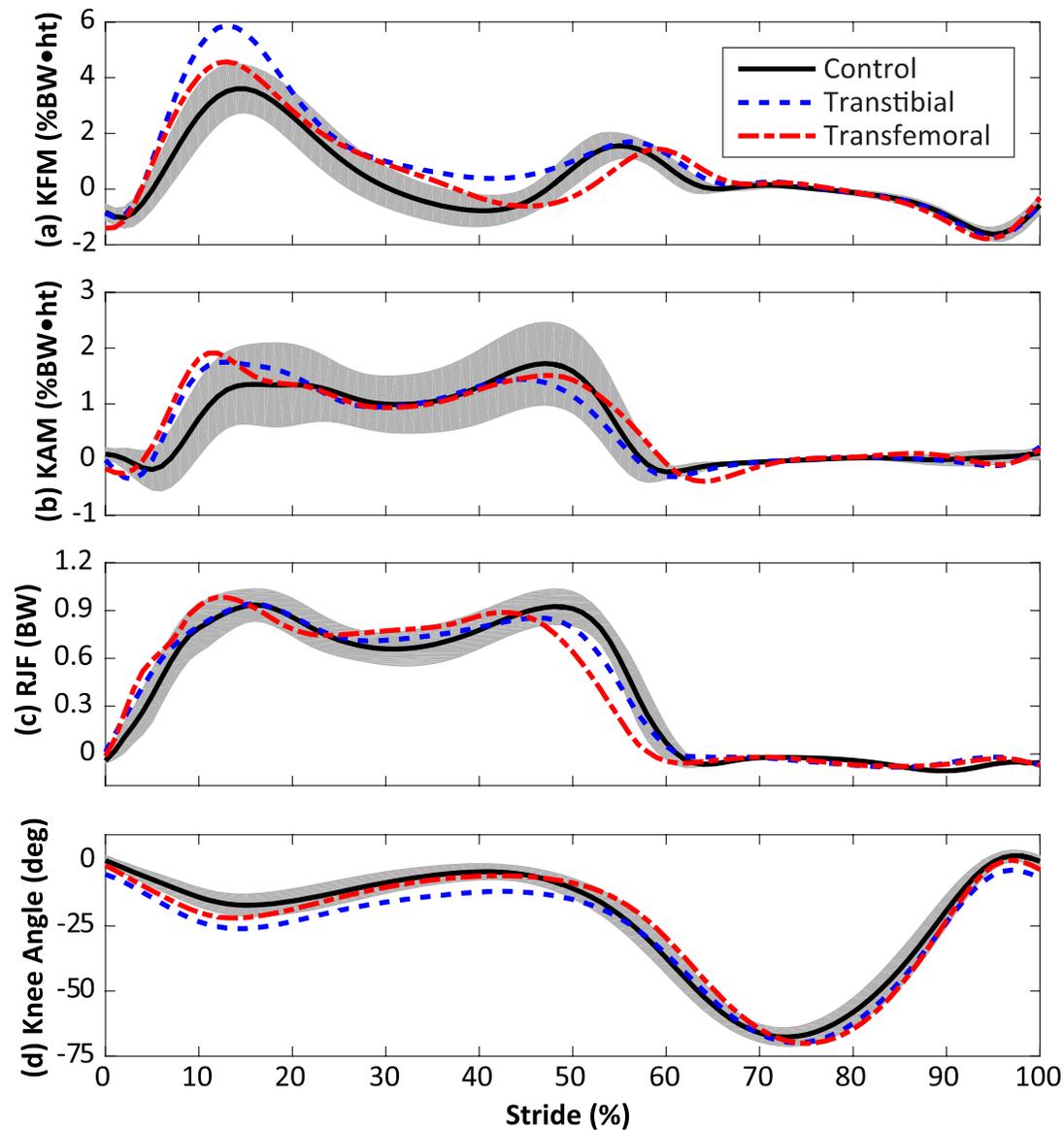


572
573
574
575
576

Figure 4. Means \pm one between-subjects standard deviation for peak (a), loading rate (b), and impulse (c) of the medial knee joint contact force for the transtibial subjects (TTA), the transfemoral subjects (TFA), and the control subjects. The limb loss bars (LL) are data for the TTA and TFA subjects combined. * = greater than control, with a large effect size ($d > 0.80$).



577
578 **Figure 5.** Monte Carlo simulation results for knee model parameter perturbations. The vertical
579 axis shows the fraction of iterations for which the medial joint contact force outcome variable
580 was significantly greater in the limb loss group vs. the control group. The results using the
581 original (unperturbed) parameters are not included here.



582

583 **Figure 6.** Knee flexion moment (KFM, a), knee adduction moment (KAM, b), resultant joint
584 force along the long axis of the shank (RJF, c), and knee flexion angle (d) during the stride,
585 beginning at heel-strike. Solid, dashed, and dash-dotted lines are means for control, transtibial,
586 and transfemoral subjects. The shaded areas are \pm one between-subjects standard deviation for
587 the control subjects. Scaling factors were bodyweight (BW) and height (ht).

588 **Table 1.** Medial joint contact force model parameters. PCSA is physiological cross-sectional
 589 areas. The three values shown for each moment arm and each muscle angle are values at (0, -30,
 590 -60) degrees of knee flexion, respectively, with 0 degrees defined as full extension. Muscle
 591 angles are clockwise from the tibial plateau (anterior-positive and lateral-positive). Moment
 592 arms and muscle angles were defined as second-order polynomials fit to these data.

PCSA (cm²)	Value	Arnold et al. (2010)
Biceps femoris	16.8	
Semimembranosus	19.1	
Semitendinosus	4.9	
Lateral gastrocnemius	9.9	
Medial gastrocnemius	21.4	
Sagittal moment arms (mm)		Wretenberg et al. (1996)
Biceps femoris	(-21.5, -22.9, -24.4)	
Semimembranosus	(-35.6, -37.6, -41.3)	
Semitendinosus	(-25.6, -26.4, -31.2)	
Lateral gastrocnemius	(-38.7, -41.0, -47.0)	
Medial gastrocnemius	(-37.9, -40.4, -47.6)	
Patellar tendon	(50.8, 50.6, 44.1)	
Frontal moment arms (mm)		Wretenberg et al. (1996)
Biceps femoris	(48.8, 48.4, 48.6)	
Semimembranosus	(-33.5, -33.7, -30.1)	
Semitendinosus	(-29.7, -30.5, -26.3)	
Lateral gastrocnemius	(19.4, 18.4, 19.2)	
Medial gastrocnemius	(-8.6, -15.1, -17.1)	
Patellar tendon	(4.7, 6.7, 9.1)	
Sagittal muscle angles (deg)		Wretenberg et al. (1996)
Biceps femoris	(89.6, 88.9, 89.3)	
Semimembranosus	(107.5, 100.3, 98.7)	
Semitendinosus	(105.6, 96.9, 96.6)	
Lateral gastrocnemius	(73.7, 65.6, 61.3)	
Medial gastrocnemius	(74.0, 67.9, 64.3)	
Patellar tendon	(63.8, 58.5, 56.2)	
Frontal muscle angles (deg)		Wretenberg et al. (1996)
Biceps femoris	(102.0, 100.6, 100.9)	
Semimembranosus	(84.2, 83.8, 85.3)	
Semitendinosus	(84.7, 89.1, 89.4)	
Lateral gastrocnemius	(85.7, 84.7, 86.1)	
Medial gastrocnemius	(83.9, 82.0, 78.8)	
Patellar tendon	(101.3, 98.0, 95.7)	
Distance b/w femoral condyles (cm)	5.0	Terzidis et al. (2012)

593