### 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 <sup>Corresp., 1, 2</sup>, Rebecca L Krupenevich <sup>1</sup>, Alison L Pruziner <sup>1, 3, 4</sup>, Erik J Wolf <sup>3, 4</sup>, Barri L Schnall <sup>3</sup>

<sup>1</sup> Department of Kinesiology, University of Maryland, College Park, Maryland, United States

<sup>2</sup> Neuroscience & Cognitive Science Program, University of Maryland, College Park, Maryland, United States

<sup>3</sup> Walter Reed National Military Medical Center, Bethesda, Maryland, United States

<sup>4</sup> 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  $27\pm5$  years,  $170\pm36$  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  $30\pm4$  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.

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#### 5 Authors:

- 6 Ross H. Miller<sup>1,2</sup> (corresponding author)
- 7 Rebecca L. Krupenevich<sup>1</sup>
- 8 Alison L. Pruziner<sup>1,3,4</sup>
- 9 Erik J. Wolf<sup>3,4</sup>
- 10 Barri L. Schnall<sup>4</sup>
- 11
- 12 <sup>1</sup>Department of Kinesiology, University of Maryland, College Park, MD, USA
- 13 <sup>2</sup>Neuroscience & Cognitive Science Program, University of Maryland, College Park, MD, USA
- <sup>3</sup>DoD-VA Extremity Trauma and Amputation Center of Excellence
- 15 <sup>4</sup>Walter 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).
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- **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.
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- 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 injuries involving major limb loss (Fischer, 2015). Individuals with unilateral lower limb loss 46 47 have a high risk of developing secondary physical conditions later in life, including osteoarthritis (OA) in their intact limb (Gailey et al., 2008; Morgenroth et al., 2012). In veterans with 48 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 models (Jurvelin et al., 1986). The time when unilateral limb loss patients first begin walking 74 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 $\pm$ SD) were: age 27 $\pm$ 5 years, height 1.77 $\pm$ 0.05 m, mass 81.1 $\pm$ 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 23 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. Individual markers 125 were attached by double-sided tape on the anterior- and posterior-superior iliac spines, iliac 126 crests, greater trochanters, medial and lateral femoral epicondyles, medial and lateral malleoli, 127 heads of the 2nd and 5th metatarsals, and heel of the shoe. Lightweight shells with clusters of 128 four markers were attached to the thigh and shank using elastic wraps. The medial markers were 129 removed after a standing calibration trial and were reconstructed as virtual markers during the 130 walking trials.

131

#### 132 Protocol

Subjects walked along the walkway at self-selected speed and cadence. Instructions were
to walk in a "normal and comfortable" fashion. Each subject walked back and forth along the
walkway until five acceptable trials were collected, with "acceptable" defined as each foot

- 136 contained entirely within the bounds of a single force platform and both feet never
- 137 simultaneously contacting the same platform.
- 138

#### 139 Data Processing

140 Marker positions and GRF from each trial were exported to Visual3D (C-Motion, 141 Germantown, MD, USA) for further analysis. Marker positions and GRF were smoothed using a 142 4th-order dual-pass Butterworth filter with cutoff frequencies of 6 Hz and 50 Hz, respectively. A linked-segment model of each subject's pelvis and intact limb was defined using marker 143 144 positions from a standing calibration trial. The hip joint center was estimated from the positions 145 of the pelvis markers (Bell et al., 1989). The knee center was estimated as the midpoint of the 146 femoral condyle markers, and the ankle joint center was estimated as the midpoint of the malleoli 147 markers. The long axes of the thigh and shank were defined between the proximal and distal joint centers. The frontal plane axis for both segments was defined from the cross-product of the 148 149 long axis and the vector between the femoral condyles. The sagittal plane axis was the cross-150 product of the frontal plane and long axes. Segment tracking during gait trials was calculated 151 from the positions of marker clusters on rigid shells. Joint angles during gait were calculated using 6DOF pose estimation, with a Cardan Xyz 152

rotation sequence (Wu & Cavanagh, 1995). Resultant joint forces and moments were calculated
by iterative Newton-Euler inverse dynamics beginning at the foot (Selbie et al., 2014). The
resultant knee forces and moments were expressed in the shank reference frame.

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#### 157 Joint Contact Force Modeling

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158 Medial knee joint contact forces were calculated using the model of Schipplein and 159 Andriacchi (1991). Muscle moment arms and orientations were defined as quadratic functions of 160 the knee flexion angle using average values for men from Wretenberg et al. (1996). The KFM 161 was assumed to be produced by the quadriceps if the moment was extensor, by the hamstrings if 162 the moment was flexor in swing or during early stance, and by the gastrocnemius if the moment 163 was flexor in late stance. Forces in the individual hamstrings muscles (biceps femoris, 164 semimembranosus, semitendinosus) and the two gastrocnemius heads were distributed by the 165 ratios of their physiological cross-sectional areas from Arnold et al. (2010). The medial contact 166 force was then calculated by balancing the frontal plane moments about the lateral contact point 167 (Fig. 1). Cruciate and collateral ligament forces were included in the contact force calculation 168 using the method described by Morrison (1968). The distance between the medial and lateral 169 tibiofemoral contact points in the frontal plane was assumed to be 5.0 cm on average and was 170 scaled linearly for each subject by the distance between the medial and lateral femoral condyle 171 markers during the standing calibration trial. Baseline model parameters are summarized in 172 Table 1.

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

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179 Statistical Analysis

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180 The planned comparisons were the peak, loading rate, and impulse of the contact force 181 between groups. These outcome variables were scaled by bodyweight (BW), with the mass of 182 the prosthesis included in this calculation for the limb loss subjects. Loading rate was defined as 183 the maximum loading rate during 10-90% of the time from heel-strike until the first peak. 184 Results will be presented for the transibilation and transfermoral subjects separately. 185 However, due to the small sample sizes, these subjects were combined into a single limb loss 186 group for statistical comparison with the control group. It will be seen that the differences in 187 contact forces between the limb loss and control groups were not driven by the transtibial or 188 transfemoral subjects specifically (i.e. contact forces were similar on average for transtibial and 189 transfemoral subjects). 190 Normality of the outcome variables was assessed using Kolmogorov-Smirnov tests. All

191 tests passed at the  $\alpha = 0.05$  level. Subsequently, comparisons between groups were made using 192 independent Student's *t*-tests ( $\alpha = 0.05$ ,  $\beta = 0.20$ ) with a False Discover Rate adjustment for the 193 multiple outcome variables. The tests were one-tailed due to the directional nature of the 194 hypothesis. 95% confidence intervals (CI) were also calculated. As an additional conservative 195 check due to the small sample sizes, differences were reported only if the effect size was large 196 (Cohen's d > 0.80). Effect sizes for between-subjects differences in external knee adduction 197 moment (a common surrogate for medial joint loading) and knee OA initiation and progression 198 are typically much smaller than 0.8 (e.g. Amin et al., 2004; Miyazaki et al., 2002), so the 199 requirement of a large effect size is likely a fairly conservative check.

200

201 Sensitivity Analysis

202 The knee model (Fig. 1) required input parameters for muscle moment arms, orientations, 203 and physiological cross-sectional areas, and the distance between the tibiofemoral contact points. 204 The necessary imaging data to define these parameters on a subject-specific basis were not 205 available, and the same generic parameter values were used for all subjects except for the contact 206 point distance. In such situations, probabilistic approaches are useful for assessing the sensitivity 207 of model output to parameter value uncertainty (Valero-Cuevas et al., 2009). To assess the 208 sensitivity of the contact force results (and the conclusions drawn from them) to these parameter 209 values, standard normal distributions were formed for each parameter with the nominal value as 210 the mean and a coefficient of variation of 10%, which is a reasonable estimate of the typical 211 variation in these parameters in a homogenous adult male population (Hasson & Caldwell, 2012). The contact force variables were then re-calculated for each subject using parameters 212 213 randomly drawn from these distributions, and the statistical analysis was performed again. This 214 process was repeated iteratively until the fraction of iterations with significantly greater outcome 215 variables in the limb loss group changed by under 1% over 100 further iterations. The output of 216 this analysis was the fraction of perturbed parameter sets for which the outcome variable in 217 question (peak, loading rate, or impulse) was greater in the limb loss group, from which the 218 sensitivity of the outcome variables to the assumed model parameters could be judged.

219

#### 220 RESULTS

Subject-specific data including descriptors, outcome variables, and waveforms of knee joint kinetics, kinematics, and medial contact forces, are included in the supplementary material. The self-selected walking speeds were similar between groups  $(1.25\pm0.19 \text{ m/s} \text{ for limb loss},$  $1.31\pm0.10 \text{ m/s}$  for controls, p = 0.40, d = 0.39, 95%CI = (-0.19, 0.07) m/s). Stride durations were

225 also similar between groups  $(1.16\pm0.07 \text{ s for limb loss}, 1.12\pm0.07 \text{ s for controls}, p = 0.24, d =$ 226 0.55, 95%CI = (-0.02, 0.10) s). The average medial knee joint contact force waveforms are 227 shown for the transformed, and control subjects in Fig. 2. The contact forces showed 228 the typical two-peaked pattern seen in instrumented knee replacement studies of older adults 229 without limb loss (Walter et al., 2010; Kutzner et al., 2013; Meyer et al., 2013). For the control 230 subjects, the peak force occurred in early stance and averaged 1.57±0.26 BW, which is within 231 the range of values reported in these studies (1.25-2.20 BW). With the exception of a lack of 232 quadriceps activity in late swing, which did not affect the contact force outcome variables, the 233 muscle forces predicted by the model for the quadriceps, hamstrings, and gastrocnemius (Fig. 3) 234 were consistent with normative electromyogram timing for these muscles (Sutherland, 2001; 235 Sevedali et al., 2012).

236 The peak contact force was greater in the limb loss group than in the control group 237  $(1.84\pm0.37 \text{ vs. } 1.57\pm0.26 \text{ BW}, p = 0.037, d = 0.85, 95\%\text{CI} = (-0.01, 0.55) \text{ BW})$ . Maximum 238 loading rate was also greater in the limb loss group (24.7 $\pm$ 5.4 vs. 19.9 $\pm$ 3.2 BW/s, p = 0.012, d =239 1.10, 95%CI = (1.0, 8.7) BW/s). Impulse had a moderate effect size between groups, but were 240 not significantly greater in the limb loss group  $(0.72\pm0.12 \text{ BW} \cdot \text{s} \text{ for limb loss}, 0.64\pm0.13 \text{ BW} \cdot \text{s})$ for controls, p = 0.084, d = 0.64, 95%CI = (-0.03, 0.19) BW•s). Outcome variables are 241 242 summarized in Fig. 4. The sensitivity analysis converged after about 3,000 iterations (Fig. 5). 243 The loading rate, peak, and impulse were greater in the limb loss group than in the control group 244 (p < 0.05, d > 0.80) for 98%, 73%, and 25% of these iterations, respectively.

The KAM and KFM were not analyzed statistically due to concerns over multiple comparisons with small sample sizes, and the fact that both variables were considered in the calculation of contact forces, but their mean profiles are presented for completeness in Fig. 6.

Limb loss subjects tended to have greater peak KFM and KAM than the control subjects, and the transtibial subjects tended to have greater peak KFM than the transfemoral subjects. The primary mechanism by which the transtibial and transfemoral subjects had similar peak contact forces (Fig. 2) despite greater KFM in the transtibial subjects was greater axial resultant joint force in the transfemoral subjects during early stance (Fig. 6).

253

#### 254 **DISCUSSION**

255 In this study we tested the hypothesis that knee joint loading during walking is greater in 256 the intact limb of US Military service members with unilateral limb loss who are relatively 257 young, recently ambulatory, and otherwise healthy, compared to the limbs of service members 258 with similar demographics and no limb loss. Based on the nominal contact force results (Fig. 4) 259 and the probabilistic analysis of model parameters (Fig. 5), we accept this hypothesis with a high 260 degree of confidence based on the loading rate of the medial joint contact force, and with a 261 moderate degree of confidence based on the peak of the medial joint contact force. Impulse of 262 the contact force did not appear to be greater in the limb loss group.

263 Before discussing the implications of these results, we first comment on some limitations. 264 The study included small sample sizes, with a mix of transibilation and transfermoral subjects (five 265 each) in the limb loss group. However, the transtibial and transfemoral subjects had similar average height, mass, and self-selected walking speeds (differences of 0.4 cm, 2.8 kg, and 0.02 266 267 m/s, respectively), and it can be seen from Fig. 4 that they also had similar contact force results, 268 suggesting that combining these sub-groups into one group was reasonable for the purposes of 269 this study. The limb loss population is difficult to study in large numbers, and we were working 270 with a particular subset of this population (young service members and some fairly restrictive

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271 additional inclusion criteria). Due to the small sample size, we took a conservative approach to 272 reporting differences between groups even after adjusting for multiple comparisons, with the 273 requirement of a large effect size. The issues of the knee model parameters and antagonistic co-274 contraction have already been addressed: these modeling issues may affect the numerical values 275 of the results, but would be unlikely to change the conclusions (Fig. 5). The knee contact model 276 itself (Fig. 1) is a Morrison (1968)-type reduction approach. These models are on the lower end 277 of complexity among the range of musculoskeletal models used for this purpose, but have a long 278 history in biomechanics (Morrison, 1968; Schipplein & Andriacchi, 1991; DeVita & Hortobágyi, 279 2001; Messier et al., 2011; Willy et al., 2016). History/popularity alone do not validate the 280 approach, but this approach produces similar muscle forces to more mathematically intensive 281 static optimization methods (Kernozek et al., 2016) and knee contact forces in good agreement 282 with instrumented knee replacement measurements (Willy et al., 2016).

283 The time point at which the gait data were obtained from the limb loss group (shortly 284 after they became independently mobile) could be viewed as a limitation since the gait 285 mechanics of these individuals may change in the future. Although the knee kinetics in the 286 present limb loss subjects (Fig. 6) are similar to those in studies on more experienced prosthesis 287 users (Royer & Koenig, 2005; Russell Esposito & Wilken, 2014), the data here may not 288 represent the "typical" or "average" loads these subjects will experience later in life, due for 289 example to motor learning, experience, changes in fitness, or use of different prostheses. 290 However, the focus on joint loading early on in the rehabilitation process can also be viewed as a 291 strength of the present study. Human articular cartilage appears to undergo at least some degree 292 of structural and functional atrophy in the absence of mechanical loading, and it is unclear if 293 these changes are fully reversible (Vanwanseele et al., 2002; Hudelmaeir et al., 2006; Souza et

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al., 2012; Owman et al., 2014). When new prosthesis users first begin walking independently,
their joints have likely undergone a period of at least several weeks with no or minimal
mechanical loading following injury, surgery, and recovery. At this early time, we speculate that
placing abnormal loads on the intact limb may be particularly dangerous for the future health of
the knee. To minimize this risk, we suggest that long periods of unloading should be avoided to
the extent that doing so is safe and feasible for the patient.

300 To the knowledge of the authors, the present study is the first to show that medial knee 301 joint contact forces were greater in the intact limb than in controls. A recent forward dynamics 302 simulation study showed a similar result for the total joint contact force during walking in 303 individuals with unilateral transtibial limb loss (Silverman & Neptune, 2014). Knee OA has a 304 rising incidence among young United States military service members over the past 10 years, 305 and there is a need to develop more effective preventive strategies in at-risk sub-groups of this 306 population (Showery et al., 2016). There are presently no longitudinal studies on baseline joint 307 loading and the initiation of knee OA in the limb loss population. However, Morgenroth et al. 308 (2014) found that the KAM peak, impulse, and loading rate were all significantly correlated with 309 the degree of knee structural abnormality present in the intact limb of middle-aged adults (mean 310 age 56 years) with unilateral transfermoral amputations. The present results suggest that 311 relatively high loads are present on the medial knee of the intact limb when young service 312 members with limb loss begin to walk independently, and when interpreted in light of 313 Morgenroth et al. (2014), that the long-term consequence of these loads may be structural degeneration of the knee. These suggestions are in need of verification in longitudinal studies. 314 315 Relatedly, while the present results suggest medial knee joint loading was greater in the 316 limb loss group, the size of the "minimum meaningful difference" that actually affects the risk

317 for knee OA is unknown. Studies using the external knee adduction moment suggest that effect 318 sizes for differences in medial joint loading during walking and the initiation and progression 319 knee OA in older adults may be small (Amin et al., 2004; Miyazaki et al., 2002), but it is 320 unknown if this suggestion generalized to actual medial joint contact forces or to a younger 321 military limb loss population. Two recent studies suggest that the "minimum detectable change" 322 in medial knee joint loading from gait modification is about 0.25-0.30 BW for peak and about 323 0.04 BW•s for impulse (Gardinier et al., 2013; Barrios & Willson, 2016). Those data were from within-subject designs, where the present data are between-subjects, but they suggest that 324 325 differences smaller than these values may be difficult to reliably detect in gait analysis, even if 326 they are biologically meaningful. For reference, the average differences between the limb loss 327 and control results in the present study were 0.27 BW for peak and 0.08 BW s for impulse. 328 Additional knowledge from longitudinal studies is needed to understand which features of joint 329 loading and cartilage mechanics are most important for predicting future structural degeneration, 330 and if critical thresholds for those variables exist.

331 As noted earlier, the KAM is presently the most popular variable for assessing medial 332 knee joint loading in human gait. While we did not analyze the KAM statistically due to 333 concerns over the small sample sizes and multiple comparisons, visual inspection of the KAM 334 (Fig. 6) suggests that similar conclusions would have been reached had we used the KAM rather 335 than the medial joint contact force as the primary outcome variable: greater peak and greater 336 loading rate in the limb loss group. However, we caution that this result was likely coincidental 337 and is not a mechanical requirement. The KAM alone does not dictate the loading of the medial 338 knee, as recent instrumented knee implant studies have shown (Walter et al., 2010; Kutzner et 339 al., 2013; Meyer et al., 2013). Relatedly, the KFM has a major influence on the shape,

340 magnitude, and medial/lateral ratio of joint contact forces, and should be considered when

341 assessing joint loading in gait (Manal et al., 2015).

342

#### 343 CONCLUSIONS

344 In summary, the present results suggest that young, recently ambulatory service members

345 with unilateral limb loss place relatively high loads on their medial knee when walking compared

346 to controls without limb loss. We suggest these loads may be a risk factor for future

347 development of knee OA, a common secondary condition in this population. Further

348 longitudinal study and development of preventive interventions (e.g. physical activity guidelines,

349 prosthesis designs) is warranted. The results also indicate that knee contact model parameter

350 values can be an important consideration in cross-sectional studies. Here we investigated the

351 overall sensitivity (perturbing all contact model parameters simultaneously), but sensitivity to

352 particular parameters of interest may be a relevant topic for future work or specific applications.

353

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358

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





567 **Stride (%)** 568 **Figure 2.** Medial knee joint contact forces in percent bodyweight (BW) during the stride,

beginning at heel-strike. Solid, dashed, and dash-dotted lines are means for control, transtibial,

570 and transfermoral subjects. The shaded areas are  $\pm$  one between-subjects standard deviation for

571 the control subjects.



572 573 Figure 3. Calculated muscle forces for the quadriceps (Quads, a), hamstrings (Hams, b), and 574 gastrocnemius (Gastroc, c) muscles during the stride, beginning at heel-strike. Solid, dashed, 575 and dash-dotted lines are means for control, transtibial, and transfemoral subjects. The shaded 576 areas are  $\pm$  one between-subjects standard deviation for the control subjects. Scaling factors 577 were bodyweight (BW). The black bars along the top of each panel denote the fraction(s) of the 578 gait cycle when this muscle group is "on" according to normative electromyograms (Sutherland, 579 2001), which are similar for the intact limb in limb loss subjects (Seyedali et al., 2012).

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585 Iterations
 586 Figure 5. Monte Carlo simulation results for knee model parameter perturbations. The vertical

axis shows the fraction of iterations for which the medial joint contact force outcome variable

was significantly greater in the limb loss group vs. the control group. The results using the

589 original (unperturbed) parameters are not included here.



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Figure 6. Knee flexion moment (KFM, a), knee adduction moment (KAM, b), resultant joint force along the long axis of the shank (RJF, c), and knee flexion angle (d) during the stride, 592 593 beginning at heel-strike. Solid, dashed, and dash-dotted lines are means for control, transtibial, and transfermoral subjects. The shaded areas are  $\pm$  one between-subjects standard deviation for 594 595 the control subjects. Scaling factors were bodyweight (BW) and height (ht).

**Table 1.** Medial joint contact force model parameters. PCSA is physiological cross-sectional

597 areas. The three values shown for each moment arm and each muscle angle are values at (0, -30,

-60) degrees of knee flexion, respectively, with 0 degrees defined as full extension. Muscle

angles are clockwise from the tibial plateau (anterior-positive and lateral-positive). Moment

600 arms and muscle angles were defined as second-order polynomials fit to these data.

PCSA (cm <sup>2</sup> )	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)

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