

# UCSF

## UC San Francisco Previously Published Works

### Title

Ground reaction force patterns in knees with and without radiographic osteoarthritis and pain: descriptive analyses of a large cohort (the Multicenter Osteoarthritis Study)

### Permalink

<https://escholarship.org/uc/item/77h6h4n3>

### Journal

Osteoarthritis and Cartilage, 29(8)

### ISSN

1063-4584

### Authors

Costello, KE  
Felson, DT  
Neogi, T  
[et al.](#)

### Publication Date

2021-08-01

### DOI

10.1016/j.joca.2021.03.009

Peer reviewed



Published in final edited form as:

*Osteoarthritis Cartilage*. 2021 August ; 29(8): 1138–1146. doi:10.1016/j.joca.2021.03.009.

## Ground reaction force patterns in knees with and without radiographic osteoarthritis and pain: descriptive analyses of a large cohort (the Multicenter Osteoarthritis Study)

Kerry E. Costello<sup>1,2</sup>, David T. Felson<sup>2</sup>, Tuhina Neogi<sup>2</sup>, Neil A. Segal<sup>3,4</sup>, Cora E. Lewis<sup>5</sup>, K. Douglas Gross<sup>6</sup>, Michael C. Nevitt<sup>7</sup>, Cara L. Lewis<sup>1,2</sup>, Deepak Kumar<sup>1,2</sup>

<sup>1</sup>Boston University, Boston, MA

<sup>2</sup>Boston University School of Medicine, Boston, MA

<sup>3</sup>University of Kansas Medical Center, Kansas City, KS

<sup>4</sup>The University of Iowa, Iowa City, IA

<sup>5</sup>University of Alabama at Birmingham, Birmingham, AL

<sup>6</sup>MGH Institute of Health Professions, Boston, MA

<sup>7</sup>University of California at San Francisco, San Francisco, CA

### Abstract

**Objective**—To compare ground reaction force patterns (GRF) during walking among legs defined by presence or absence of knee pain and/or radiographic knee osteoarthritis (ROA).

**Method**—Principal component analysis extracted major modes of variation (PCs) in GRF data from the Multicenter Osteoarthritis Study during self-paced walking. Legs were categorized as pain+ROA (n=168), ROA only (n=303), pain only (n=476), or control (n=1877). Relationships between group and GRF PCs were examined using Generalized Estimating Equations, adjusted for age, sex, body mass index, race, and clinic site with and without additional adjustment for gait speed.

---

#### Author contributions

Responsibility for the integrity of the work as a whole: K.E. Costello, D. Kumar

Conception and design: K.E. Costello, D. Kumar, D.T. Felson

Analysis and interpretation of the data: All authors

Drafting of the article: K.E. Costello, D. Kumar

Critical revision of the article for important intellectual content: All authors

Final approval of the article: All authors

Provision of study materials or patients: D.T. Felson, C.E. Lewis, M.D. Nevitt, N.A. Segal

Obtaining of funding: D.T. Felson, D. Kumar, C.E. Lewis, C.L. Lewis, T. Neogi, M.D. Nevitt

**Publisher's Disclaimer:** This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

#### Competing interest statement

The authors have no professional relationships with companies or manufacturers who will benefit from the results of the present study. NAS reports personal fees from Springer and grants from Flexion Therapeutics, Pacira CyroHealth, Zimmer-Biomet, and Tenex Health, outside of the submitted work.

**Results**—With or without speed adjustment, pain+ROA had flatter vertical GRF waveforms than control (speed adjusted PC2 difference [95%CI]: -66 [-113,-20]), pain+ROA and ROA only had higher lateral GRF at impact and greater mid-stance medial GRF than control (speed adjusted PC3 difference: 9 [3,16] and 6 [2,10], respectively), and ROA only had higher early versus late medial GRF than control (speed adjusted PC2 difference: 7 [2,13]). Pain only had flatter vertical GRF waveforms and a smaller difference between anterior and posterior GRF than control only without speed adjustment.

**Conclusion**—In this large sample, sustained mid-stance loading and higher impact loads were identified in legs with ROA or ROA and pain, even when adjusting for differences in gait speed and other confounders. While it remains to be seen whether these features precede or result from ROA and pain, the presence of these patterns in the speed-adjusted models could have implications on gait interventions aimed to change joint loading.

### Keywords

Knee; ground reaction force; pain; radiographic osteoarthritis; principal component analysis

---

### Introduction

Mechanical loading has been implicated in knee osteoarthritis (OA) pathogenesis, suggesting that interventions aimed at changing joint loading may be key to reducing the burden of knee OA<sup>1</sup>. Knee OA is characterized by radiographic damage and clinical symptoms, particularly knee pain, however, individuals may have knee pain without radiographic damage or vice versa<sup>2</sup>. Prior research suggests that risk factors may differ for these clinical phenotypes<sup>3</sup>, however, their association with joint loading, specifically gait patterns during walking, is not well understood.

Traditionally, gait differences among individuals with and without knee OA have been compared using specific, discrete metrics extracted from gait waveforms, such as a peak or impulse. While between group differences have been identified with these approaches (e.g., peak knee angle and moment differences across OA severities<sup>4</sup>), differences in the patterns of loading have also been noted<sup>5, 6</sup>. These patterns are challenging to capture with discrete metrics but may better describe the overall loading environment experienced by the joint. For example, the so-called “stiff gait” pattern – used to describe gait features including reduced sagittal plane range of motion, reduced peak to peak sagittal plane moments, prolonged muscle activation in mid-stance, and/or the absence of a characteristic bimodal (“double-hump”) pattern in the knee adduction moment (KAM) and frontal plane ground reaction force (GRF) – has been associated with greater knee OA severity<sup>7</sup> and future disease progression<sup>8</sup>. Investigating these dynamic loading patterns, rather than merely discrete metrics, may provide better understanding of the relationships among gait, pain, and radiographic disease (ROA).

Assessment of the relationships among gait, pain, and ROA can be confounded by factors such as age<sup>9</sup>, body mass index (BMI)<sup>10</sup>, sex<sup>11</sup>, and race<sup>12</sup>, which are risk factors for knee OA and can affect gait independent of OA. Furthermore, gait speed presents a challenge in analyses as it is associated with both gait metrics and OA outcomes but its role in the causal

pathway is unclear<sup>13</sup>. Adjusting for gait speed may remove confounding effects if it is indeed a confounder (affecting both gait and OA outcomes), however, OA outcomes, such as pain, may drive changes in gait speed rather than vice versa. Thus, bias could be introduced by adjusting for gait speed, leading to inappropriate conclusions about the relationships between gait and OA outcomes. To account for confounders and explore the effect of adjusting for speed on the relationships among gait, pain, and ROA, larger sample sizes than those of prior studies (approximately 20 to 200 participants or legs<sup>14</sup>) are required. While collection of joint moment data is resource and time-intensive, GRFs can be collected with relative ease in large cohorts, are a main component used to calculate knee joint moments, and follow similar patterns of variation during gait as joint moments (e.g., the bimodal pattern seen in both the frontal plane GRF and KAM)<sup>15</sup>. Examining differences in GRFs in a large cohort could further clarify the role of abnormal mechanics in knee OA pathogenesis.

The objective of this descriptive study was to quantify cross-sectional differences in dynamic GRF patterns during walking between groups of knees defined by presence or absence of both knee pain during walking and radiographic knee OA while accounting for multiple confounders.

## Method

### Study sample

The data used in this study are from the Multicenter Osteoarthritis Study (MOST)<sup>16</sup>. MOST is a prospective, NIH-funded cohort study of risk factors for the incidence and progression of OA and includes two clinic sites in the United States: The University of Alabama at Birmingham and The University of Iowa. The original cohort (age = 50–79, with or at increased risk for developing knee OA) was enrolled in 2003–2005 and followed for 80 months. At 144-months, surviving participants from the original cohort were invited to return for a clinic visit. Concurrently, a new cohort (age 45–69, with or without knee pain, and with Kellgren-Lawrence radiographic grades  $\geq 2$ ) was enrolled, such that the baseline visit for the new cohort corresponded with the 144-month visit of the original cohort. Participants with inflammatory disease or stroke were not included in either cohort. The MOST study received institutional review board approval from the two clinical centers as well as the coordinating center at the University of California San Francisco and the analysis center at Boston University. In accordance with the Helsinki Declaration, all participants provided informed consent prior to participating in the study.

We utilized GRF data from both cohorts (original cohort at 144-month, new cohort at baseline) for the current analyses (Figure 1). Participants with a history of knee or hip replacement or steroid or hyaluronic acid injection in either knee during the past 6 months were excluded. This combined sample included individuals with and without knee OA and knee pain.

### Categorization of legs using knee pain and radiographic knee OA

Posterior-anterior and lateral weight bearing radiographs taken at the 144-month/baseline timepoint were read for Kellgren-Lawrence grade (KLG) of the tibiofemoral joint at the

MOST analysis center. Knees with KLG  $\geq 2$  were considered to have radiographic tibiofemoral knee OA (ROA). For each knee, presence of knee pain was defined by participants' self-report of at least mild pain during walking over the past 30 days using question 1 of the Western Ontario and McMaster Universities Osteoarthritis: "How much pain do you have in your left/right knee while walking on a flat surface?" We then categorized each knee into one of four groups: (1) pain+ROA, (2) ROA only, (3) pain only, or (4) control (i.e., no pain and no ROA).

### Ground reaction force data collection

Three-dimensional GRF data were recorded at 1000 Hz using a portable force platform and AccuGait walkway (AMTI Inc., Watertown, MA, USA). Participants walked along the 5.3-meter walkway at self-selected speed wearing their own typical footwear. Approximately five trials of GRF data were acquired from each leg of each participant. The first trial for each leg was considered an acclimatization trial and excluded.

Legs with at least three remaining trials where the foot landed completely on the force plate and a corresponding gait speed measurement was available were retained for analysis. For each leg, raw, unfiltered GRF waveforms were time-normalized to the stance phase of the gait cycle and ensemble averaged across three randomly selected remaining trials.

### Ground reaction force data processing

Principal component analysis (PCA) was applied to extract the main modes of variation (principal components, PCs) among GRF waveforms in each dimension: vertical, anterior-posterior, and medial-lateral<sup>17</sup>. For each dimension, the data were arranged into a matrix ( $X = [n \times 101]$ ), with each row representing the ensemble average GRF across trials of an individual leg. To preserve the assumption of independence of observations, data from only one randomly selected leg per person was used to extract PCs, thus only one leg per person was included in this matrix. After subtracting the mean of  $X$  from each row, an eigenvector decomposition was performed on the covariance matrix of  $X$  to extract the eigenvectors (PCs). PCs that cumulatively explained 90% of the variation among the waveforms for each dimension were retained for analysis. For all legs, including those not used to extract the PCs, eigenvalues (PC scores) for each dimension were calculated as:  $PC \text{ scores} = (GRF_{\text{Ens. Avg.}} - \text{mean}(X)) * \text{PCs}$ . The PC scores for each leg describe how closely the waveforms matched each retained PC. To aid in interpretation, the percent variance explained at every percent of the gait cycle by each PC was plotted. In addition, single PC reconstructions were created for the 5<sup>th</sup>, 33<sup>rd</sup>, 50<sup>th</sup>, 67<sup>th</sup>, and 95<sup>th</sup> percentile PC scores among waveforms included in the extraction of eigenvectors by multiplying the PC by the PC score, respectively, and adding this product to the mean of  $X$ <sup>18</sup>.

### Statistical analysis

We examined the relationships between group (pain+ROA, ROA only, pain only, and control) and GRF PC scores in separate models for each PC using Generalized Estimating Equations (GEEs) to account for correlations between two legs within an individual. Analyses were performed adjusted for sex, age, BMI, race, and clinic site, both with and without additional adjustment for gait speed. All models were first constructed including an

interaction term between group and leg. If this interaction term was not significant, it was removed from the model. A significant effect of group in the model was assessed using a Wald Chi Square test. Estimated marginal means were calculated for each group. Post-hoc, Wald Chi Square tests were performed for all pairwise comparisons among groups for any PC that had a significant omnibus test for group. All analyses were performed in SPSS (version 26.0.0.1, IBM, Armonk, NY, USA) with significance set at  $\alpha = 0.05$ . No adjustment for multiple comparisons was performed because all examined associations were biologically plausible and adjustment for multiple comparisons in exploratory analyses may eliminate meaningful associations<sup>19</sup>.

## Results

Data from 2824 legs contributed by 1576 individuals were included in these analyses (Table 1). This sample included 168 legs with pain and ROA (pain+ROA), 303 legs with ROA but no pain (ROA only), 476 legs with pain but not ROA (pain only), and 1877 control legs without pain or ROA. Individual leg waveforms are presented in Supplementary Figure S1 to show the variety of waveform patterns within the sample.

Across the three GRF dimensions, 11 PCs were retained in total (Table 2). The interaction term between group and leg was not significant for any of the analyses and thus was removed from the models. In the models that did not adjust for gait speed, significant group differences were found for four PCs across the three GRF dimensions: vertical GRF PC2 ( $p = 0.001$ ), anterior-posterior GRF PC1 ( $p = 0.025$ ), medial-lateral GRF PC2 ( $p = 0.015$ ), and medial-lateral GRF PC3 ( $p = 0.002$ ). In the analyses that additionally adjusted for gait speed, a significant group effect remained for vertical GRF PC2 ( $p = 0.041$ ), medial-lateral GRF PC2 ( $p = 0.025$ ), and medial-lateral GRF PC3 ( $p = 0.002$ ), but not anterior-posterior GRF PC1 ( $p = 0.239$ ). Estimated marginal mean PC scores (both adjusted and unadjusted for gait speed) for all four groups are presented in Supplementary Table S1.

### Vertical Ground Reaction Force

While the differences among groups in the unadjusted vertical GRF waveforms (Figure 2A) are small, in the analyses that adjusted for confounders (but did not adjust for speed), legs with pain (pain+ROA and pain only) had flatter vertical GRF waveforms with lower peaks and higher mid-stance force (i.e., lower vertical PC2 scores, Figure 2B,2D) than legs without pain (ROA only and control). When we additionally adjusted for gait speed, legs with pain +ROA had lower scores (i.e., flatter waveforms) than all other groups (Figure 2C,2D) but there were no other differences in vertical PC2 scores among groups.

### Anterior-Posterior Ground Reaction Force

Between-group differences in anterior-posterior GRFs were barely visible on the unadjusted group waveforms (Figure 3A) but when adjusted for confounders (but not speed), pain only legs had a smaller difference between early and late stance anterior-posterior GRF (i.e., lower anterior-posterior PC1 scores Figure 3B,3D) than ROA only legs ( $p = 0.009$ ) and control legs ( $p = 0.016$ ). This difference in anterior-posterior PC1 among groups was only present when not adjusting for speed (Figure 3C,3D).

## Medial-Lateral Ground Reaction Force

Again, between group differences in the unadjusted medial-lateral GRF waveforms appeared small (Figure 4A), however, ROA only legs had higher early relative to late stance medial GRF (i.e., higher medial-lateral PC2 scores, Figure 4B–4D) compared to pain only or control legs, when adjusted for confounders both with additional adjustment for speed ( $p = 0.012$  and  $p = 0.005$ , respectively) and without ( $p = 0.002$  and  $p = 0.007$ , respectively). Additionally, both groups of legs with ROA (pain+ROA and ROA only) had higher magnitude lateral peak force in early and late stance with higher medial force in mid-stance (i.e., higher medial-lateral PC3 scores, Figure 4E–4G) compared to groups of legs without ROA (pain only and control) when adjusted for confounders. This relationship was present regardless of whether speed was included in the analysis ( $p < 0.01$  for all described comparisons).

## Discussion

By utilizing the large MOST cohort, the objective of this study was to examine the relationships among GRF patterns, knee pain, and ROA while accounting for confounding due to sex, age, BMI, and race, both with and without additional adjustment for gait speed. We identified multiple pattern differences in three-dimensional GRFs among groups, including sustained and higher impact loading patterns. Both sustained and higher loads could result in poor outcomes over the long-term and have implications on interventions.

Differences among groups in vertical PC2, describing a less dynamic vertical GRF pattern with flattening through mid-stance in those with lower scores, were identified in both the models that did and did not adjust for speed. As cyclic loading and unloading during dynamic weight-bearing activities is critical for maintaining articular tissue health<sup>20</sup>, a sustained, constant loading pattern could indicate potentially detrimental overload of articular tissues. Without adjustment for gait speed, painful legs (pain+ROA and pain only) had less dynamic vertical GRF than legs without pain (ROA only and control), in agreement with previous work showing less dynamic loading patterns in individuals with painful OA compared to pain-free individuals<sup>7</sup> and in healthy individuals after induction of knee pain<sup>21</sup>. Prior work has also identified this flattened vertical GRF pattern in midstance in females with painful knee OA compared to controls without OA<sup>22, 23</sup>. With adjustment for gait speed, however, legs with pain+ROA had a less dynamic vertical GRF than all other groups. Prior work by Boyer et al. has suggested joint inflammation in those with painful ROA, rather than pain alone, may drive gait changes. In this cross-over study of individuals with knee OA, vertical GRF increased following treatment with nonsteroidal anti-inflammatory drugs (NSAID) when compared to placebo, but did not increase following treatment with opioids, suggesting the anti-inflammatory component of NSAIDs rather than the analgesic component of both drugs was the reason for GRF changes<sup>24</sup>. Thus, the presence of this flattened GRF pattern in the pain+ROA group but not the pain only group in the speed-adjusted model could potentially be explained by differences in inflammation between the groups.

While it is unclear from the current cross-sectional study design whether these gait patterns precede or result from the development of painful ROA, these results suggest potentially

detrimental loading in knees with pain+ROA. The vertical ground reaction force is a main component of the KAM<sup>25</sup> and sustained loading in KAM during mid-stance has been associated with future total knee arthroplasty<sup>8</sup>. Further, these findings suggest that this less dynamic vertical GRF pattern in the pain+ROA group could not be altered with interventions that target gait speed, as it remained after adjusting for speed.

Gait speed interventions also appear unlikely to change medial-lateral GRF patterns as the same between-group differences were present in both the speed-adjusted and unadjusted analyses. These included a higher ratio of early to late medial force (medial-lateral PC2) in ROA only legs compared to legs without ROA (pain only or control) and higher lateral peaks in early and late stance with higher mid-stance medial force (medial-lateral PC3) in legs with ROA (both pain+ROA and ROA only) compared to legs without ROA (pain only or control). Along with the vertical ground reaction force and lever arm of the knee, the medial-lateral ground reaction force is a key component of the KAM<sup>25</sup>. Thus, a higher ratio of early to late medial-lateral force could result in higher KAM in early stance, which has been associated with both future structural OA progression<sup>26–29</sup> and future total knee arthroplasty<sup>30</sup>. High impact load has been shown to result in bone and/or cartilage changes indicative of osteoarthritis development in both animal models<sup>31</sup> and tissue explants<sup>32</sup>, thus the lateral impact force captured by medial-lateral PC3 could also indicate potentially harmful loading on ROA compared to no ROA legs. Again, the cross-sectional nature of the current study does not indicate whether these impact loading patterns precede or result from the development of structural damage but their presence in both the speed-adjusted and unadjusted models suggests interventions other than altering gait speed would be needed to change these potentially detrimental loading patterns. Furthermore, the higher medial loads through mid-stance (captured by medial-lateral PC3) could again be indicative of potentially detrimental, sustained loading in mid-stance.

In contrast, differences among groups in anterior-posterior GRFs appeared to be driven by speed as there was no effect of group in the models that adjusted for speed. The smaller difference between anterior and posterior GRF (PC1) in legs with pain compared to legs without pain (control or ROA only) may reflect an attempt to reduce pain by walking at a slower speed. It should also be noted that despite greater variability in the pain+ROA legs in this measure, the mean difference between pain+ROA and control legs in anterior-posterior PC1 was similar to the difference between pain and control legs (Figure 3B), again suggesting pain may be driving this gait pattern.

The appropriateness of adjusting for speed has been debated<sup>13</sup>, as decreasing speed is associated with the disease process and thus adjusting for speed may remove some of the effects of the disease and introduce bias due to conditioning on an intermediate. However, GRF magnitude can be affected by gait speed. While an examination of causal relationships was not part of the current study design, the differences in GRF patterns that remained after adjusting for speed indicates there are some aspects of gait patterns in knee OA that are unaffected by gait speed. If these aspects are related to longitudinal OA outcomes, they would likely require gait interventions other than merely addressing slow gait speeds. Further research could investigate modifiable factors that may be related with these patterns



(e.g., muscle power, inter-joint coordination) which could be targeted with interventions such as neuromuscular training.

Strengths of the current study include the use of a large dataset from a well characterized cohort, which, unlike prior, smaller gait studies, allowed us to control for a number of confounding factors, and the use of three-dimensional GRFs and principal component analysis to explore multi-dimensional loading patterns. A number of limitations of the current analyses should also be acknowledged. While it has been demonstrated that gait patterns vary across severities of both ROA and pain<sup>33</sup>, we utilized dichotomous definitions of ROA and pain to categorize legs, which did not allow for an examination of differences in GRFs related to severity of ROA and/or pain. Second, our analyses did not consider presence of predominantly medial, lateral, or patellofemoral radiographic OA or pain. Hence, these findings, particularly those related to medial-lateral GRFs, should be interpreted with caution as GRF patterns may differ between those with radiographic disease or pain in different compartments. It should also be noted that while the GEEs allowed us to account for correlation between legs in the analyses, the analysis approach does not allow investigation of how unilateral versus bilateral ROA or pain affects GRF patterns. Prior work has previously reported gait differences in those with unilateral versus bilateral OA<sup>34</sup>, however, the specific GRF patterns in a leg with ROA only and contralateral ROA+pain versus a contralateral control leg, for example, are still unclear and will be relevant to understanding progression trajectories in the two legs of a person. Participants in the current study wore their own, typical footwear, which may have increased inter-subject variability in GRF waveforms, however, as individuals will likely wear their own footwear during daily life, we believe this represents a more clinically relevant measure of GRF data. Last, while PCA allows examination of GRF patterns, it can also result in retained PCs that describe variability among waveforms due to factors other than the factor of interest (e.g., vertical PC1 likely captures magnitude differences related to body mass). Features explaining a small amount of variance may be useful in discriminating among groups<sup>35</sup>, however, it remains to be seen whether these features which describe only a small portion of the variance among waveforms in the current study are related to longitudinal OA outcomes. A minimal clinically important difference in these PC scores has yet to be determined.

In this large sample of legs with and without radiographic knee OA and pain, after adjusting for confounders, a number of differences in GRF patterns were identified that suggest altered loading in legs with ROA or ROA and pain. While it remains to be seen whether these features precede or result from ROA and pain, the sustained mid-stance loading and higher peak lateral forces seen in these groups could indicate potentially detrimental loading at the knee. Importantly, these pattern differences are present even in the speed-adjusted models, which could have implications on intervention strategies aimed at changing joint loading.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

The authors would like to acknowledge the contributions of the MOST participants and clinic staff. Matlab file exchange software was utilized to create the figures: Scott Lowe (2021) superbar (<https://github.com/scottclowe/superbar>), GitHub. Retrieved January 28, 2021.

### Role of the funding source

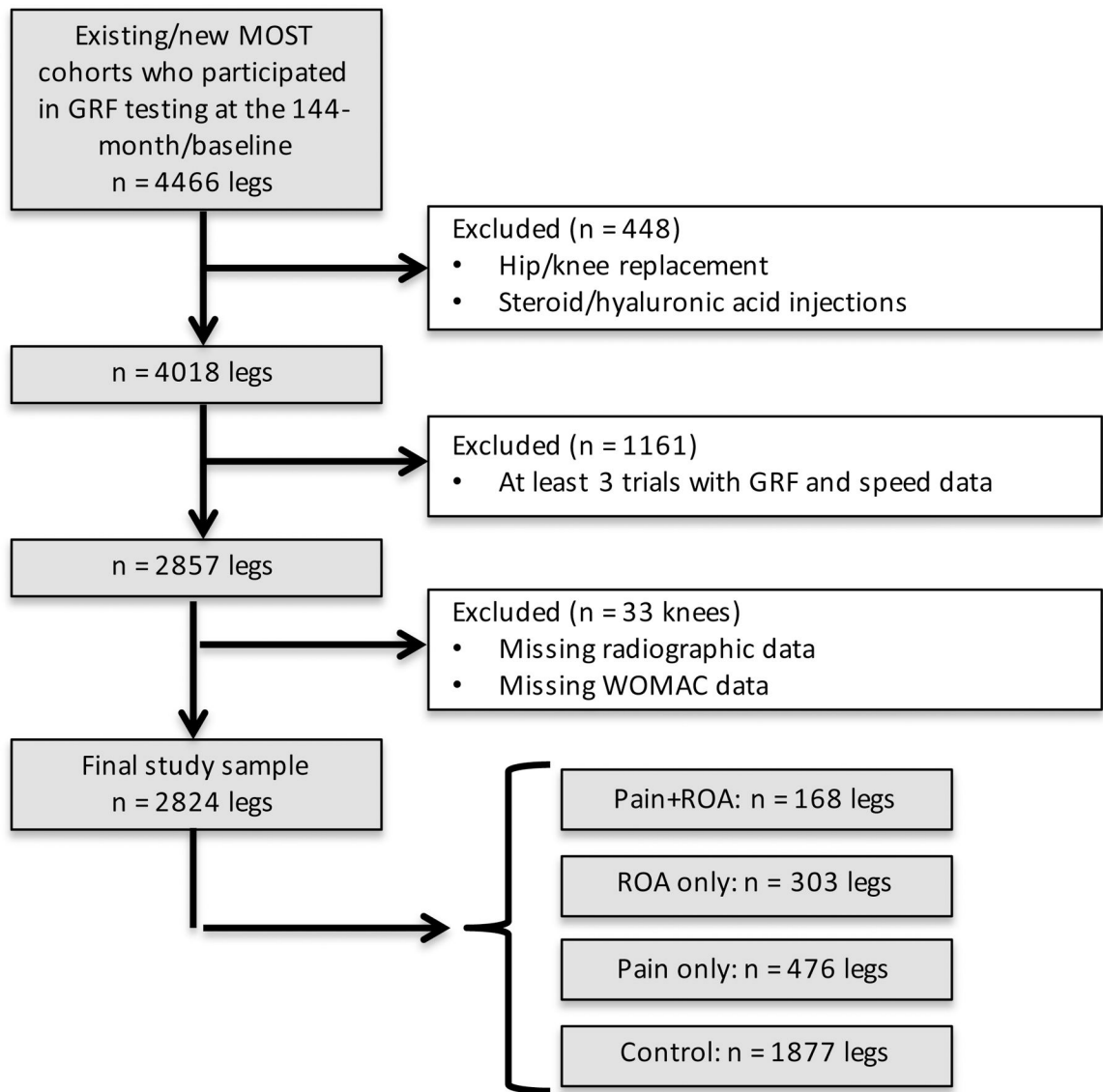
MOST is comprised of four cooperative grants [D.T. Felson (BU) – AG18820, J.C. Torner (UI) – AG18832, C.E. Lewis (UAB) – AG18947, and M.C. Nevitt (UCSF) – AG19069] funded by the National Institutes of Health (NIH), a branch of the Department of Health and Human Services, and conducted by MOST study investigators. Research reported in this publication was also supported under award numbers K01AR069720 (D. Kumar), K23AR063235 (C.L. Lewis), K24AR070892 (T. Neogi), P30AR07257101A1 (D.T. Felson), 1UL1TR001430 (D.T. Felson), T32AR00759820 (D.T. Felson), and F32AR076907 (K.E. Costello) from the National Institutes of Health. This manuscript was prepared using MOST data and does not necessarily represent the official views of MOST investigators or the National Institutes of Health. The MOST publications committee reviewed this manuscript before submission. The National Institutes of Health was not involved in study design, collection, analysis or interpretation of data, or the decision to submit this manuscript for publication.

## References

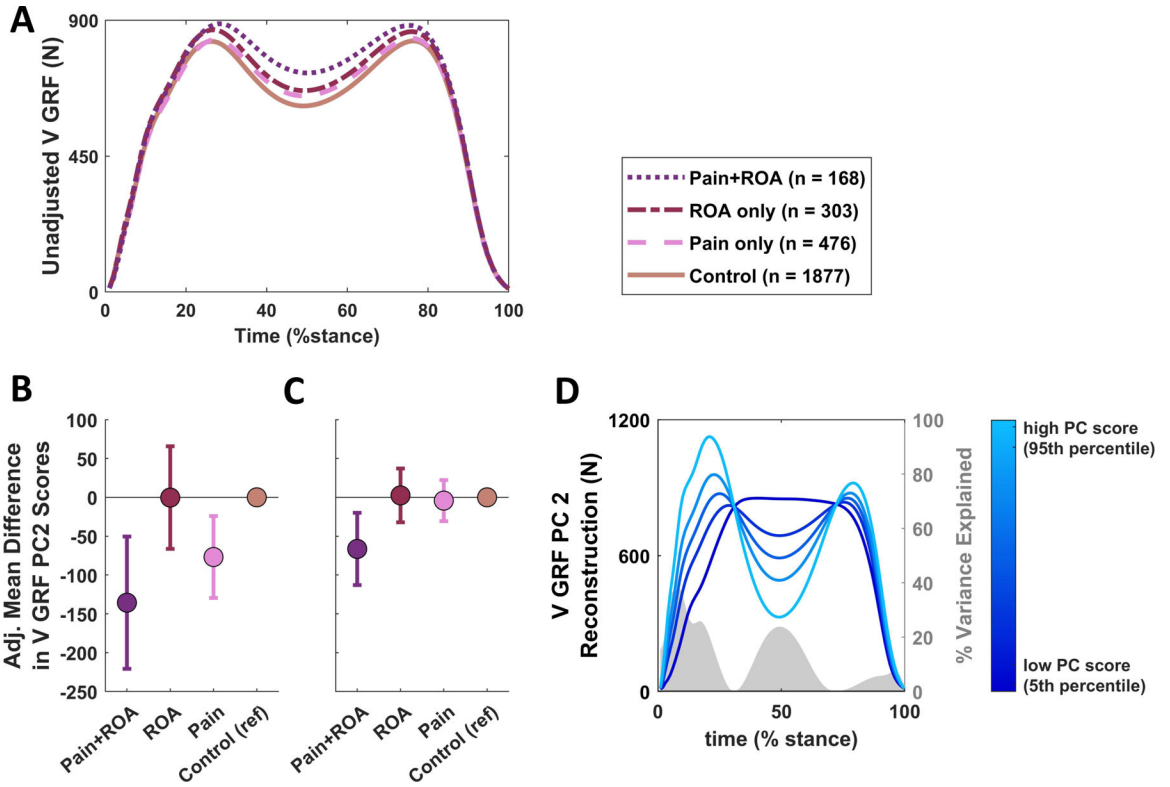
1. Felson DT. Osteoarthritis as a disease of mechanics. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2013; 21: 10–5. DOI: 10.1016/j.joca.2012.09.012.
2. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC musculoskeletal disorders* 2008; 9. DOI: 10.1186/1471-2474-9-116.
3. Zhang Y, Jordan JM. Epidemiology of osteoarthritis. *Clin Geriatr Med* 2010; 26: 355–69. DOI: 10.1016/j.cger.2010.03.001. [PubMed: 20699159]
4. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 2008; 26: 332–41. DOI: 10.1002/jor.20496. [PubMed: 17960658]
5. Astephen JL, Deluzio KJ. A multivariate gait data analysis technique: application to knee osteoarthritis. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine* 2004; 218: 271–9
6. Federolf PA, Boyer KA, Andriacchi TP. Application of principal component analysis in clinical gait research: identification of systematic differences between healthy and medial knee-osteoarthritic gait. *J Biomech* 2013; 46: 2173–8. DOI: 10.1016/j.jbiomech.2013.06.032. [PubMed: 23910389]
7. Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ, Hubley-Kozey CL. Gait and neuromuscular pattern changes are associated with differences in knee osteoarthritis severity levels. *Journal of Biomechanics* 2008; 41: 868–76. DOI: 10.1016/j.jbiomech.2007.10.016. [PubMed: 18078943]
8. Hatfield GL, Stanish WD, Hubley-Kozey CL. Three-dimensional biomechanical gait characteristics at baseline are associated with progression to total knee arthroplasty. *Arthritis Care Res (Hoboken)* 2015; 67: 1004–14. DOI: 10.1002/acr.22564. [PubMed: 25708360]
9. Duffell LD, Jordan SJ, Cobb JP, McGregor AH. Gait adaptations with aging in healthy participants and people with knee-joint osteoarthritis. *Gait & posture* 2017; 57: 246–51. DOI: 10.1016/j.gaitpost.2017.06.015. [PubMed: 28672154]
10. Harding GT, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Astephen JL. Body mass index affects knee joint mechanics during gait differently with and without moderate knee osteoarthritis. *Osteoarthritis and Cartilage* 2012; 20: 1234–42. DOI: 10.1016/j.joca.2012.08.004. [PubMed: 22902710]
11. McKean KA, Landry SC, Hubley-Kozey CL, Dunbar MJ, Stanish WD, Deluzio KJ. Gender differences exist in osteoarthritic gait. *Clinical Biomechanics* 2007; 22: 400–9. DOI: 10.1016/j.clinbiomech.2006.11.006. [PubMed: 17239509]
12. Sims EL, Keefe FJ, Kraus VB, Guilak F, Queen RM, Schmitt D. Racial differences in gait mechanics associated with knee osteoarthritis. *Aging Clin. Exp. Res* 2009; 21: 463–9 [PubMed: 20154517]

13. Astephen Wilson JL. Challenges in dealing with walking speed in knee osteoarthritis gait analyses. *Clinical Biomechanics* 2012; 27: 210–2. DOI: 10.1016/j.clinbiomech.2011.09.009. [PubMed: 22019141]
14. Mills K, Hunt MA, Ferber R. Biomechanical deviations during level walking associated with knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Care Res. (Hoboken)* 2013; 65: 1643–65. DOI: 10.1002/acr.22015. [PubMed: 23554153]
15. Hunt MA, Birmingham TB, Giffin JR, Jenkyn TR. Associations among knee adduction moment, frontal plane ground reaction force, and lever arm during walking in patients with knee osteoarthritis. *J Biomech* 2006; 39: 2213–20. DOI: 10.1016/j.jbiomech.2005.07.002. [PubMed: 16168997]
16. Segal NA, Nevitt MC, Gross KD, Hietpas J, Glass NA, Lewis CE, et al. The Multicenter Osteoarthritis Study: opportunities for rehabilitation research. *PM R* 2013; 5: 647–54. DOI: 10.1016/j.pmrj.2013.04.014. [PubMed: 23953013]
17. Deluzio KJ, Astephen JL. Biomechanical features of gait waveform data associated with knee osteoarthritis: an application of principal component analysis. *Gait & posture* 2007; 25: 86–93. DOI: 10.1016/j.gaitpost.2006.01.007. [PubMed: 16567093]
18. Brandon SC, Graham RB, Almosnino S, Sadler EM, Stevenson JM, Deluzio KJ. Interpreting principal components in biomechanics: representative extremes and single component reconstruction. *Journal of electromyography and kinesiology : official journal of the International Society of Electrophysiological Kinesiology* 2013; 23: 1304–10. DOI: 10.1016/j.jelekin.2013.09.010. [PubMed: 24209874]
19. Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990; 1: 43–6 [PubMed: 2081237]
20. Griffin TM, Guilak F. The role of mechanical loading in the onset and progression of osteoarthritis. *Exerc Sport Sci Rev* 2005; 33: 195–200 [PubMed: 16239837]
21. Henriksen M, Graven-Nielsen T, Aaboe J, Andriacchi TP, Bliddal H. Gait changes in patients with knee osteoarthritis are replicated by experimental knee pain. *Arthritis Care Res (Hoboken)* 2010; 62: 501–9. DOI: 10.1002/acr.20033. [PubMed: 20391505]
22. Chen CP, Chen MJ, Pei YC, Lew HL, Wong PY, Tang SF. Sagittal plane loading response during gait in different age groups and in people with knee osteoarthritis. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 2003; 82: 307–12. DOI: 10.1097/01.PHM.0000056987.33630.56.
23. Gök H, Ergin S, Yavuzer G. Kinetic and kinematic characteristics of gait in patients with medial knee arthrosis. *Acta orthopaedica Scandinavica* 2011; 73: 647–52. DOI: 10.3109/17453670209178029.
24. Boyer KA, Angst MS, Asay J, Giori NJ, Andriacchi TP. Sensitivity of gait parameters to the effects of anti-inflammatory and opioid treatments in knee osteoarthritis patients. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 2012; 30: 1118–24. DOI: 10.1002/jor.22037. [PubMed: 22179861]
25. Hunt MA, Birmingham TB, Giffin JR, Jenkyn TR. Associations among knee adduction moment, frontal plane ground reaction force, and lever arm during walking in patients with knee osteoarthritis. *Journal of Biomechanics* 2006. DOI: 10.1016/j.jbiomech.2005.07.002.
26. Miyazaki T, Wada M, Kawahara H, Sato M, Baba H, Shimada S. Dynamic load at baseline can predict radiographic disease progression in medial compartment knee osteoarthritis. *Ann Rheum Dis* 2002; 61: 617–22. DOI: 10.1136/ard.61.7.617. [PubMed: 12079903]
27. Woollard JD, Gil AB, Sparto P, Kwok CK, Piva SR, Farrokhi S, et al. Change in knee cartilage volume in individuals completing a therapeutic exercise program for knee osteoarthritis. *J Orthop Sports Phys Ther* 2011; 41: 708–22. DOI: 10.2519/jospt.2011.3633. [PubMed: 21891881]
28. Chehab EF, Favre J, Erhart-Hledik JC, Andriacchi TP. Baseline knee adduction and flexion moments during walking are both associated with 5 year cartilage changes in patients with medial knee osteoarthritis. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2014; 22: 1833–9. DOI: 10.1016/j.joca.2014.08.009.

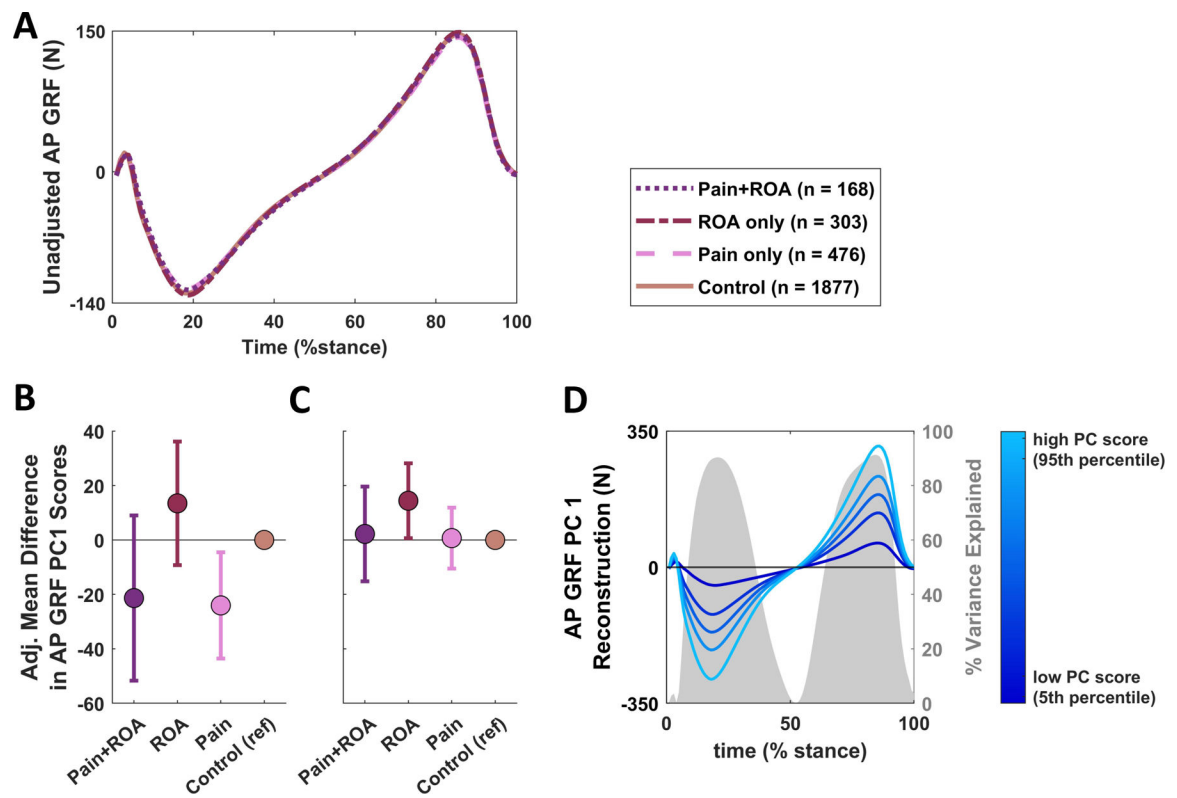
29. Chang A, Hurwitz D, Dunlop D, Song J, Cahue S, Hayes K, et al. The relationship between toe-out angle during gait and progression of medial tibiofemoral osteoarthritis. *Ann Rheum Dis* 2007; 66: 1271–5. DOI: 10.1136/ard.2006.062927. [PubMed: 17267516]
30. Hatfield GL, Stanish WD, Hubley-Kozey CL. Relationship between knee adduction moment patterns extracted using principal component analysis and discrete measures with different amplitude normalizations: Implications for knee osteoarthritis progression studies. *Clin Biomech (Bristol, Avon)* 2015; 30: 1146–52. DOI: 10.1016/j.clinbiomech.2015.08.011.
31. Radin EL, Martin RB, Burr DB, Caterson B, Boyd RD, Goodwin C. Effects of mechanical loading on the tissues of the rabbit knee. *Journal of Orthopaedic Research* 1984; 2: 221–34. DOI: 10.1002/jor.1100020303. [PubMed: 6436458]
32. Huser CA, Davies ME. Validation of an in vitro single-impact load model of the initiation of osteoarthritis-like changes in articular cartilage. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society* 2006; 24: 725–32. DOI: 10.1002/jor.20111. [PubMed: 16514652]
33. Astephen Wilson JL, Deluzio KJ, Dunbar MJ, Caldwell GE, Hubley-Kozey CL. The association between knee joint biomechanics and neuromuscular control and moderate knee osteoarthritis radiographic and pain severity. *Osteoarthritis and cartilage / OARS, Osteoarthritis Research Society* 2011; 19: 186–93. DOI: 10.1016/j.joca.2010.10.020.
34. Creaby MW, Bennell KL, Hunt MA. Gait differs between unilateral and bilateral knee osteoarthritis. *Archives of physical medicine and rehabilitation* 2012; 93: 822–7. DOI: 10.1016/j.apmr.2011.11.029. [PubMed: 22385873]
35. Jolliffe IT. A note on the use of principal components in regression. *Journal of the Royal Statistical Society. Series C (Applied Statistics)* 1982; 31: 300–3



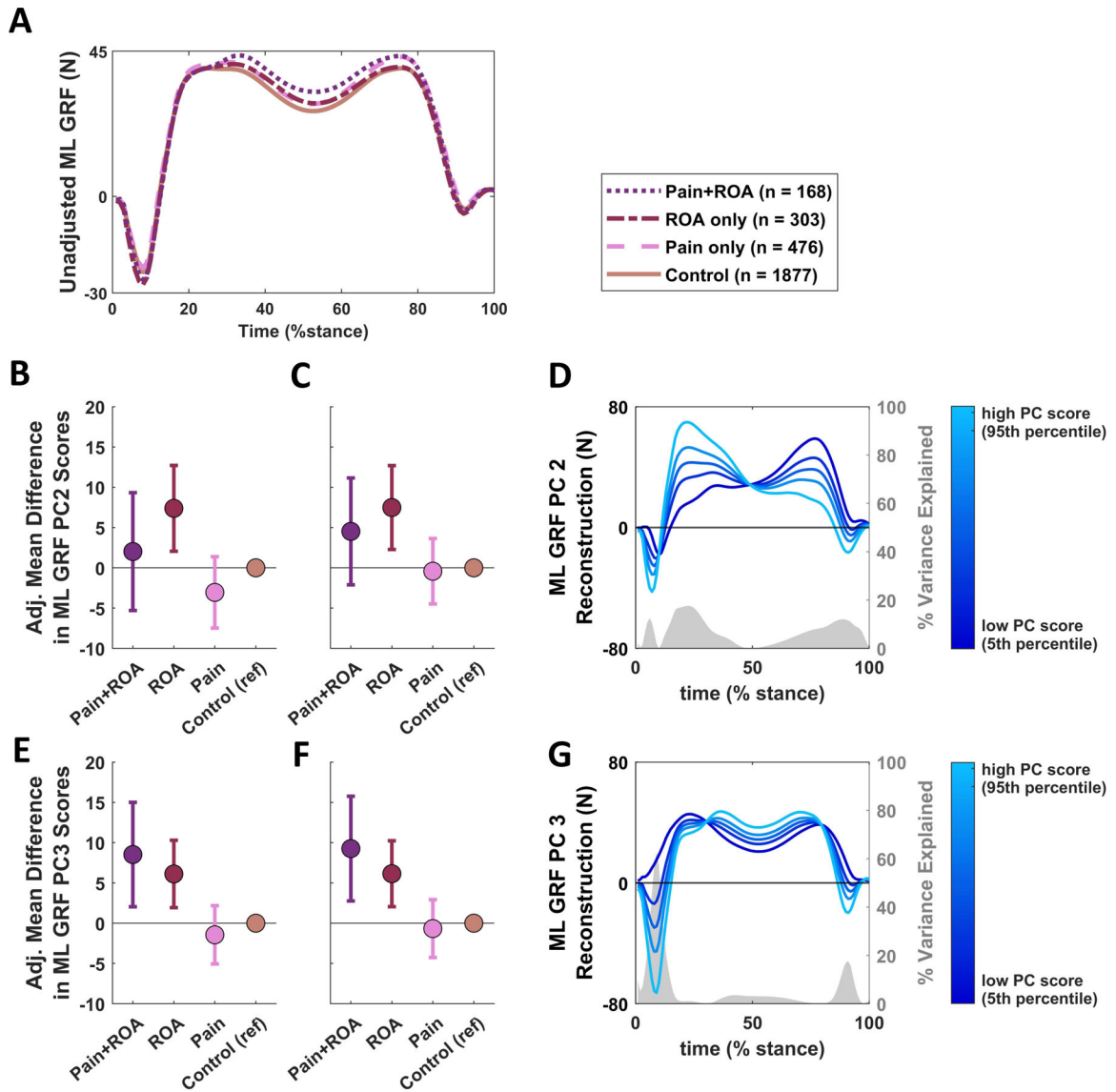
**Figure 1.** Study sample selection and groups (MOST: Multicenter Osteoarthritis Study; OA: osteoarthritis; GRF: ground reaction force; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; ROA: radiographic knee osteoarthritis).



**Figure 2.** Vertical (V) ground reaction force (GRF): [A] unadjusted V GRF for groups of legs defined by defined by presence or absence of knee pain during walking and radiographic knee osteoarthritis (ROA); [B-C] mean difference and 95% confidence intervals in estimated marginal mean V PC2 scores for groups of legs with pain and ROA, ROA only, and pain only relative to controls, adjusted for age, sex, body mass index, clinic site, race, [B] without or [C] with additional adjustment for speed; [D] waveforms reconstructed using the 5<sup>th</sup>, 33<sup>rd</sup>, 50<sup>th</sup>, 67<sup>th</sup>, or 95<sup>th</sup> percentile V PC2 score (blue lines), demonstrating how the waveform shape changes across a range of PC scores, and percent variance explained by V PC2 (shaded gray), indicating where in the stance phase the PC is capturing variance among waveforms.



**Figure 3.** Anterior-posterior (AP) ground reaction force (GRF): [A] unadjusted AP GRF for groups of legs defined by defined by presence or absence of knee pain during walking and radiographic knee osteoarthritis (ROA); [B-C] mean difference and 95% confidence intervals in estimated marginal mean AP PC1 scores for groups of legs with pain and ROA, ROA only, and pain only relative to controls, adjusted for age, sex, body mass index, clinic site, race, [B] without or [C] with additional adjustment for speed; [D] waveforms reconstructed using the 5<sup>th</sup>, 33<sup>rd</sup>, 50<sup>th</sup>, 67<sup>th</sup>, or 95<sup>th</sup> percentile AP PC1 score (blue lines), demonstrating how the waveform shape changes across a range of PC scores, and percent variance explained by AP PC1 (shaded gray), indicating where in the stance phase the PC is capturing variance among waveforms.



**Figure 4.** Medial-lateral (ML) ground reaction force (GRF): [A] unadjusted ML GRF for groups of legs defined by defined by presence or absence of knee pain during walking and radiographic knee osteoarthritis (ROA); [B-C] mean difference and 95% confidence intervals in estimated marginal mean ML PC2 scores for groups of legs with pain and ROA, ROA only, and pain only relative to controls, adjusted for age, sex, body mass index, clinic site, race, [B] without or [C] with additional adjustment for speed; [D] waveforms reconstructed using the 5<sup>th</sup>, 33<sup>rd</sup>, 50<sup>th</sup>, 67<sup>th</sup>, or 95<sup>th</sup> percentile ML PC2 score (blue lines), demonstrating how the waveform shape changes across a range of PC scores, and percent variance explained by ML PC2 (shaded gray), indicating where in the stance phase the PC is capturing variance among waveforms; [E-F] mean difference and 95% confidence intervals in estimated marginal mean ML PC3 scores for groups of legs with pain and ROA, ROA only, and pain only relative to controls, adjusted for age, sex, body mass index, clinic site, race, [E] without or [F] with additional adjustment for speed; [D] waveforms reconstructed



using the 5<sup>th</sup>, 33<sup>rd</sup>, 50<sup>th</sup>, 67<sup>th</sup>, or 95<sup>th</sup> percentile ML PC3 score (blue lines) and percent variance explained by ML PC3 (shaded gray), across the stance phase.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

**Table 1.**

## Sample Characteristics

	Full sample characteristics	Group characteristics <sup>*</sup>			
		Pain + ROA	ROA only	Pain only	Control
Sample size, n participants [n legs]	1576 [2824]	140 [168]	252 [303]	372 [476]	1192 [1877]
Sex, n participants (%)					
Female	910 (57.7%)	89 (63.6%)	155 (61.5%)	227 (61.0%)	676 (56.7%)
Male	666 (42.3%)	51 (36.4%)	97 (38.5%)	145 (39.0%)	516 (43.3%)
Site, n participants (%)					
University of Alabama at Birmingham	669 (42.4%)	66 (47.1%)	77 (30.6%)	194 (52.2%)	487 (40.9%)
University of Iowa	907 (57.6%)	74 (52.9%)	175 (69.4%)	178 (47.8%)	705 (59.1%)
Race, n participants (%)					
Black or African-American	226 (14.3%)	26 (18.6%)	29 (11.5%)	79 (21.2%)	148 (12.4%)
White or Caucasian	1297 (82.3%)	111 (79.3%)	221 (87.7%)	284 (76.3%)	998 (83.7%)
Other <sup>†</sup>	53 (3.4%)	3 (2.1%)	2 (0.8%)	9 (2.4%)	46 (3.9%)
Age (years), mean ± stdev of all participants	60.1 ± 9.1	64.9 ± 9.9	65.2 ± 9.3	58.6 ± 8.1	59.4 ± 8.9
Body mass index (kg/m <sup>2</sup> ), mean ± stdev of all participants	28.4 ± 5.2	31.1 ± 5.4	29.8 ± 5.2	28.8 ± 5.5	28.0 ± 4.9
Gait speed (m/s), mean ± stdev of all legs	1.3 ± 0.2	1.2 ± 0.2	1.3 ± 0.2	1.3 ± 0.2	1.4 ± 0.2

\* Group characteristic data presented for informational purposes only to aid in interpretation of analyses that were adjusted for a number of these factors. Note: because groups are defined by leg, a person could be included in more than one group. Analyses were adjusted for correlation between legs.

<sup>†</sup> Includes: American Indian or Alaskan Native, Asian, Hawaiian or other Pacific Islander, other race, more than one race, don't know/refused

**Table 2.**

Principal components (PCs) extracted from vertical (V), anterior-posterior (AP), and medial-lateral (ML) ground reaction forces (GRF), suggested interpretations of each PC, and variance explained by each PC.

<b>GRF Principal Components</b>		<b>Var. Exp.</b>
V1	Overall shape/magnitude (higher score indicates greater overall magnitude throughout stance)	80%
V2	Difference between mid-stance and early/late stance (higher score indicates more dynamic pattern with higher peaks in early and late stance and a lower mid-stance valley)	12%
AP1	Difference between early (braking phase) and late (propulsive phase) stance magnitude (higher score indicates greater difference between early and late stance magnitude)	74%
AP2	Phase shift (higher score indicates the waveform is shifted to later in stance)	8%
AP3	Magnitude difference in early, mid, and especially late stance (higher score indicates smaller early stance magnitude, higher mid-stance magnitude, and higher, earlier late stance magnitude)	5%
AP4	Waveform timing (higher score indicates a “wider” waveform with earlier/steeper early stance force and later, steeper, late stance force)	4%
ML1	Overall magnitude (higher score indicates more medial GRF through stance)	69%
ML2	Difference between early/late stance (higher score indicates higher medial peak in early relative to late stance)	8%
ML3	Magnitude of initial and final contact peaks and mid-stance (higher score indicates a higher magnitude lateral peak force just after foot strike and higher magnitude lateral peak force just before foot off with higher medial mid-stance magnitude)	6%
ML4	Timing of initial contact peaks (higher score indicates earlier lateral force after foot strike with earlier subsequent medial force with phase shift continuing through mid-stance resulting in lower medial magnitude in mid-stance)	5%
ML5	Shape of early medial peak and timing of unloading in late stance (higher score indicates later, higher, and distinct early medial peak as well as greater unloading in mid-stance and a phase shift of the late stance waveform to later in stance)	4%