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# Correlates and consequences of varus knee thrust in osteoarthritis

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Dissertation

**CORRELATES AND CONSEQUENCES OF VARUS KNEE THRUST IN  
OSTEOARTHRITIS**

by

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**ABSTRACT**

Varus knee thrust is an abnormal frontal-plane movement (i.e., an out-bowing) of the knee that occurs during the weight-acceptance phase of gait. Varus thrust is of clinical interest, as it is a potentially-modifiable biomechanical risk factor for knee osteoarthritis (OA) progression and has been associated with knee pain. The overall aim of this dissertation is to identify the structural and symptomatic consequences of varus thrust at the knee and along the lower limb, and the possible anatomical and sensorimotor causes of varus thrust in older adults with or at risk for OA. Varus thrust was assessed in Multicenter Osteoarthritis (MOST) Study participants using high-speed videos of self-paced walking. Varus thrust was observed in 31.3% of 3730 knees. We investigated the longitudinal relation of varus thrust to MRI lesions and found that thrust was associated with increased odds of incident and worsening bone marrow lesions and worsening cartilage loss. We then investigated the longitudinal association of varus thrust with WOMAC knee pain and found that thrust was associated with increased odds of incident and worsening total WOMAC knee pain and worsening pain during weight-bearing and non-weight bearing activities. In an ancillary quantitative gait analysis of a single subject with unilateral varus thrust, we found altered joint moments at the hip, knee, and ankle in

the thrust limb compared to the non-thrust limb. We bolstered this pilot data with an investigation of low back and lower extremity pain in the presence of thrust in MOST participants: limbs with thrust had increased odds of incident frequent pain proximal (hip or low back) and distal (ankle and foot) to the knee compared to limbs without thrust. Finally, we investigated the cross-sectional relation of anatomical and sensorimotor impairments at the knee and lower extremity to the prevalence of varus thrust. Thrust was most prevalent in limbs with static varus malalignment and supinated feet during gait, while increasing static knee laxity had a protective effect against thrust. These results fill substantial gaps in the narrative regarding the role of varus thrust in OA development.

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## LIST OF ABBREVIATIONS

<b>BML</b>	Bone Marrow Lesion
<b>BMI</b>	Body Mass Index
<b>CI</b>	Confidence Interval
<b>CPEI</b>	Center of Pressure Excursion Index
<b>EMG</b>	Electromyographic
<b>GEE</b>	Generalized Estimating Equation
<b>HKA</b>	Hip Knee Ankle
<b>ICC</b>	Intra-class Correlation Coefficient
<b>KAM</b>	Knee Adduction Moment
<b>KL</b>	Kellgren-Lawrence
<b>MRI</b>	Magnetic Resonance Imaging
<b>MOST</b>	Multicenter Osteoarthritis Study
<b>OA</b>	Osteoarthritis
<b>OR</b>	Odds Ratio
<b>ROA</b>	Radiographic Osteoarthritis
<b>VPT</b>	Vibration Perception Threshold
<b>WOMAC</b>	Western Ontario McMaster Universities
<b>WORMS</b>	Whole Organ Magnetic Resonance Imaging Score

**CHAPTER 1.**

**INTRODUCTION AND REVIEW OF THE LITERATURE**

## **Knee Osteoarthritis Epidemiology**

Osteoarthritis (OA) is a leading cause of disability and diminished quality-of-life in older adults. The knee is the weight-bearing joint most commonly affected by OA: 16% of adults over the age of 45 will develop symptomatic knee OA at some point in their lives, and this risk increases in older adults who are obese (Segal et al., 2013). OA already contributes \$185.5 billion in aggregate health care costs (Kotlarz et al., 2009), and these costs are expected to increase with the advancing age of the U.S. population and rising rates of obesity (Hootman and Helmick, 2006).

The medial compartment of the tibiofemoral joint is the most common site of knee OA. This high prevalence of medial knee OA is presumably due to thinner articular cartilage on the medial compartment and less protection from the medial meniscus, as well as loading from functional activities (Lewek et al., 2004). Women and African-Americans have a higher prevalence of lateral-compartment tibiofemoral OA (Wise et al., 2012).

## **Structural Features of Knee Osteoarthritis**

Historically, knee OA has been diagnosed using plain film radiography (Issa and Sharma, 2006). Radiological features of OA include 1) osteophyte formation on the joint margins or tibial spines, periarticular ossicles, 3) narrowing of joint cartilage associated with sclerosis of subchondral bone, 4) small pseudocystic areas with sclerotic walls situated in the subchondral bone, and 5) altered shape of bone ends (Kellgren and Lawrence, 1957). The severity of radiographic knee OA is classified using the Kellgren and Lawrence (KL) grading scale (Kellgren and Lawrence, 1957). KL grades are

determined by the presence of osteophytes and the degree of joint space narrowing—a proxy measure for cartilage loss. Conventional radiography, which offers high contrast and resolution for bone, is only a coarse measure of the structural damage associated with OA development; it cannot directly visualize non-ossified joint structures such as articular cartilage, marrow tissue, menisci, ligaments, and periarticular structures (Peterfy et al., 2004). Additionally, use of conventional radiography is not ideal for early OA detection: by the time osteophytes can be visualized, the disease process has likely been underway for years (Sharma et al., 2015).

Magnetic resonance images (MRI) are a more sensitive measure of knee structural damage. Two commonly-evaluated features are cartilage damage and bone marrow lesions (BML). Cartilage damage is described as an abnormal intracartilaginous signal or irregularities on the surface or bottom of usually smooth articular cartilage viewed on MRI (Creaby et al., 2010). BMLs are indicated by poorly-marginated areas of increased signal intensity in the normally fatty epiphyseal marrow on fat-suppressed T2-weighted magnetic resonance images (Peterfy et al., 2004) (**Figure 1.1**). These lesions are thought to represent contusions or edema within the bone marrow (Felson et al., 2001), though histopathologic examination of BML has revealed fibrosis, osteonecrosis, and extensive bony remodeling (Felson et al., 2003); these lesions are also unlikely to regress (Hunter et al., 2006). Cartilage structural damage and BMLs as visualized on MRI are typically graded using the Whole-Organ MRI Score (WORMS) for knee OA (Peterfy et al., 2004) (**Table 1.1**).

While OA is primarily considered a disease involving the loss of articular cartilage, this definition does not account for the central symptom of OA: pain. Cartilage tissue contains no pain fibers, and therefore it has been suggested that BMLs are the source of pain in osteoarthritis (Felson et al., 2001). Felson et al. (2001) reported that persons with knee pain and OA had more BMLs than persons with OA but without knee pain; however, there was no association between the lesions and the severity of pain. A subsequent longitudinal study did reveal a relationship between the increase in size of BMLs and the development of knee pain (Felson et al., 2007).



**Figure 1.1.** Two bone marrow lesions (arrow and arrowhead) seen on a T2-weighted fat-saturated sagittal MRI. Reprinted from Lo et al. “Bone marrow lesions in the knee are associated with increased local bone density.” *Arthritis & Rheumatism* 2005;52:2814-21.

**Table 1.1.**

The WOMBS scoring systems for cartilage damage and BML, from Peterfy et al. (2004)

<b>Scoring System for Cartilage Damage</b>	
<b>Grade</b>	<b>Description</b>
0	Normal thickness and signal
1	Normal thickness but increased signal on T2-weighted images
2.0	Partial-thickness focal defect < 1 cm in greatest width
2.5	Full-thickness focal defect < 1 cm in greatest width
3	Multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but < 75% of the region
4	Diffuse ( $\geq 75\%$ of the region ) partial-thickness loss
5	Multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but < 75% of the region
6	Diffuse ( $\geq 75\%$ of the region) full-thickness loss
<b>Scoring System for Sub-Regional Involvement of Bone Marrow Lesions</b>	
<b>Grade</b>	<b>Description</b>
0	None
1	$\leq 25\%$ of the sub-region
2	25-50% of the sub-region
3	$\geq 50\%$ of the sub region

### **Risk Factors for and Correlates of Knee OA**

Knee OA occurs as a results of local mechanical risk factors in the context of systemic susceptibility. Systemic factors include genetics, congenital joint deformities,

sex, age, race/ethnicity, bone mineral density, nutritional factors, and hormones, among others (Issa and Sharma, 2006; Zhang and Jordan, 2010). Mechanical factors are those factors thought to increase loading or decrease stability at the knee joint and are often the target of surgical or physical therapy interventions. These factors can be related to obesity, previous injury, or occupational physical activity (Zhang and Jordan, 2010), or they could arise from anatomical or neuromuscular insufficiencies of the lower limb. Some, but certainly not all, of these will be described in more detail below.

In the non-weight-bearing state, knee stability is provided by the ligaments, joint capsule, and other soft tissues, whereas in the weight-bearing state, stability is provided not only by interactions between ligaments and other soft tissues, but also by the geometry and congruence of the joint surfaces (i.e., the condyles), and tibiofemoral contact forces generated by muscle activity and gravitational forces (Sharma et al., 1999b; Markolf et al., 1981).

Varus-valgus knee laxity, broadly defined as knee instability or abnormal displacement or rotation of the tibia with respect to the femur, in osteoarthritic knees results from primary laxity of the capsule or ligaments; loss of cartilage or bone height (pseudolaxity); capsuloligamentous stretch resulting from malalignment; or combinations of ligamentous, meniscal, muscular, and capsular pathology (Sharma et al., 1999a). Knee laxity shifts opposing surfaces of tibiofemoral contact, reducing congruence of the joint surfaces and increasing shear and compression forces at the knee.

Varus-valgus tibiofemoral malalignment is the strongest identified risk factor for progression of knee OA, due to increased loading in one tibiofemoral joint compartment

(Issa and Sharma, 2006; Felson et al., 2013). Genu varum alters forces at the knee, shifting the line of force farther medially from the knee joint center; thus intensifying medial knee compartment loads (Lewek et al., 2004). Most osteoarthritic knees present with varus malalignment, and varus malalignment is present in a majority of total knee arthroplasties (Theinpont and Parvizi, 2016). It is important to note that static alignment, typically measured radiographically, does not represent loading under the dynamics of gait (Hunt et al., 2008).

Proprioception (or joint position sense) is broadly defined as a conscious or unconscious perception of position and movement of an extremity or a joint in space (Knoop et al., 2011). Under dynamic conditions, normal knee mechanics and functional stability depend upon proprioceptive input and reflex (Sharma et al., 1999b).

Proprioceptive information from knee mechanoreceptors is used to protect the knee against excessive and possible injurious movements by way of reflex responses (Knoop et al., 2011) or activation of agonist and antagonist muscles (Pai et al., 1997). Impaired proprioception may result in poorly controlled, excess loading to the knee during gait, initiating or accelerating joint degeneration (Felson et al., 2009). Pai et al. (1997) reported that proprioceptive acuity was decreased in knees with OA compared to age-matched controls. Proprioceptive deficits have also been linked to pain and functional limitation (Felson et al., 2009), radiographic knee OA and OA severity (Shakoor et al., 2012), and self-reported knee instability (Chang et al., 2014; Shakoor et al., 2017).

Lower extremity musculature is a natural brace for the knee joint (Segal et al., 2009). Muscles that cross the knee joint superiorly include the quadriceps femoris

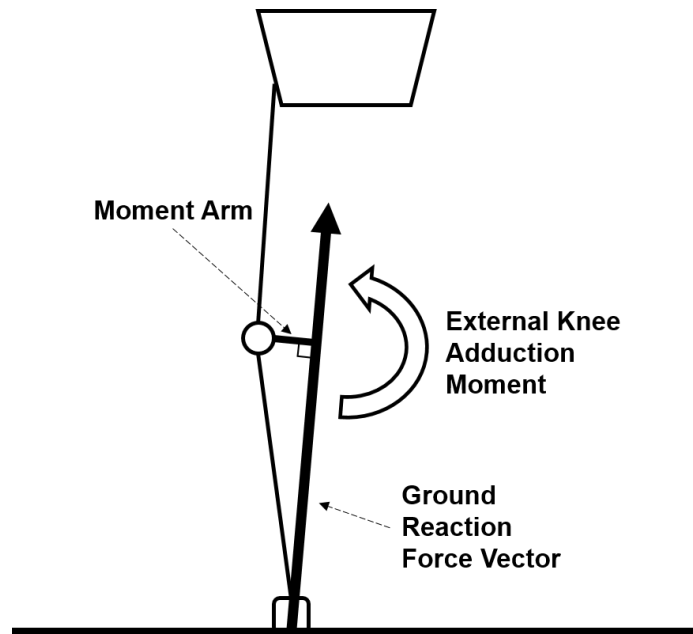
(inserting on the tibial tuberosity) anteriorly, the hamstrings (with insertions on the tibia and fibula) posteriorly, the tensor fascia lata (inserting on the lateral tibia via the iliotibial band) laterally, and the sartorius and gracilis (inserting on the medial tibia) medially. From the inferior aspect, the gastrocnemius inserts on the posterior femoral condyles. Quadriceps strength is thought to be protective against symptomatic knee OA (Segal et al., 2009, 2010b). In female OA patients, increased quadriceps weakness was found in knees with both early and established OA (Baert et al., 2013) and was associated with increased knee joint space narrowing (Segal et al., 2010a). Increased weakness of the hamstrings muscles was found in established OA patients (Baert et al., 2013). Chang et al. (2014) also found decreased varus and valgus muscle strength in OA patients compared to controls.

### **Biomechanics of Gait**

Human walking gait occurs in a cyclical pattern of multiple phases. One gait cycle, or stride, begins with initial heel strike of one foot and ends with the initial heel strike of the same foot. The stance phase, approximately 60% of the gait cycle, is the period between heel strike and ipsilateral toe-off, while the swing phase, the remaining 40% of the gait cycle, occurs while the foot is in the air. Double-limb support, the period during which both feet are in contact with the ground simultaneously, occurs during weight transfer from one limb to the other.

During normal walking, the ground reaction force passes medial to the knee and an external knee adduction moment (KAM) is applied throughout stance, transmitting most of the force through the medial compartment of the knee. The external KAM is

determined by the ground reaction force and its moment arm, which is the perpendicular distance from the ground reaction force vector to the knee joint center (Foroughi et al., 2009) (**Figure 1.2**). This moment adducts the knee toward a varus position. The external KAM is countered by an internal abduction torque created by active and passive structures, including the iliotibial band, the tensor fascia lata, and the lateral ligaments of the knee.



**Figure 1.2.** The external knee adduction moment (KAM) during stance is determined by the ground reaction force vector and its perpendicular moment arm.

Bennell et al. (2010) found an association between mechanical loading of the medial tibiofemoral compartment and medial knee OA. The external KAM is thought to be a reasonable biomechanical proxy for medial-to-lateral knee joint load distribution, given the invasive nature of measuring medial knee loads directly (Chang et al., 2015). The role of the KAM as a target for OA intervention has been of interest (e.g., Hall et al., 2017; Telfer et al., 2017). A systematic review of 14 studies by Foroughi et al. (2009)

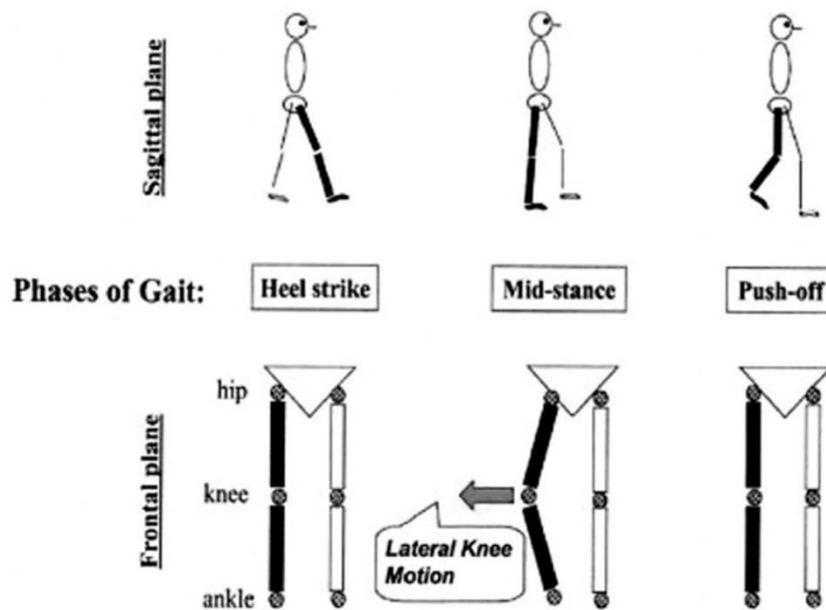
found that the external KAM was correlated with both laxity and varus malalignment. The external KAM also increased with disease severity, and in severe OA cases, was thought to be a consequence of morphological changes in the diseased joint such as medial articular cartilage loss and medial meniscus degeneration (Baert et al., 2013; Foroughi et al., 2009). There is evidence that the relationship of the external KAM to pain and physical function is dependent on disease severity (Baert et al., 2013; Hall et al., 2017).

The motion of the knee during gait is largely described as a sagittal-plane motion (i.e., flexion and extension), with slight horizontal-plane (e.g., internal/external rotation) motion occurring as a result of dynamic foot posture during gait. Substantial frontal-plane excursion of the knee during the stance phase of gait is typically limited in healthy knees (e.g., Kadaba et al., 1990). Dynamic frontal plane alignment, however, is related to compartmental loading of the tibiofemoral joint and is linked to OA disease progression (e.g., Barrios et al., 2012). Abrupt changes in frontal plane alignment occur in the form of a knee thrust.

### **Knee Thrust**

Knee thrust is defined as a dynamic frontal-plane motion (i.e., an abrupt change in alignment) of the knee during the mid-stance or weight-acceptance phase of gait, occurring in either a varus (lateral, **Figure 1.3**) or valgus (medial) direction, with a return to neutral (or less varus or valgus) alignment during the swing phase of gait. Varus thrust is more prevalent than valgus thrust among cohorts with or at risk for knee OA: the prevalence of varus thrust has ranged from 16-79% (Bennell et al., 2015; Chang et al.,

2004, 2010, 2013; Fukutani et al., 2015; Lo et al., 2012; Sosdian et al., 2016; Yoshimura et al., 2002; Wink et al., 2017), while prevalence of valgus thrust has ranged from 6-23% (Chang et al., 2010, 2013; Sosdian et al., 2016). Among persons with and without knee OA, valgus thrust was shown to be more prevalent among African Americans than Caucasians (Chang et al., 2010).



**Figure 1.3.** Varus knee thrust in mid-stance. Reprinted from Chang et al. “Thrust during ambulation and the progression of osteoarthritis” *Arthritis & Rheumatism* 2004;**50**:3897-903.

### *Biomechanical Relevance of Knee Thrust*

Several studies have detected a relationship between varus thrust and the external KAM, namely, that knees with thrust have a higher external KAM compared to knees without thrust (Chang et al., 2004; Mahmoudian et al., 2016) and that there is a positive correlation between the amount of varus thrust in degrees and the magnitude of the external KAM (Kuroyanagi et al., 2012). In addition to its association with the KAM,

varus thrust presence visualized during gait was also associated with greater mean peak angular velocity during stance and a greater peak varus angle during stance (Chang et al., 2013).

#### *Clinical Relevance of Knee Thrust*

Thrust is a well-known biomechanical risk factor for knee OA. The effect of varus thrust on knee OA was first reported by Chang et al. in 2004: a varus thrust visualized during gait was associated with a four-fold increased likelihood of medial knee OA progression over 18 months. Within varus-aligned knees, thrust was associated with a three-fold increased likelihood of OA progression (Chang et al., 2004). Lo et al. (2012) found that knees with thrust had at least four times the odds of prevalent Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain during weight bearing compared to knees without a thrust. Iijima et al. (2015) demonstrated that varus thrust, with or without static varus malalignment was associated with knee pain during gait, and Fukutani et al. (2016) found a statistically-significant association between thrust and pain and stiffness measured with the Japanese Knee Osteoarthritis Index.

The relationship between valgus thrust and knee OA has not been thoroughly studied, due to the low prevalence of valgus thrust compared to varus thrust. Chang et al. (2010) theorized that a valgus thrust would transmit load to the lateral tibiofemoral compartment, potentially increasing the risk of lateral OA disease onset and progression.

#### *Assessment of Knee Thrust*

Knee thrust has historically been assessed through both visual observation and quantitative biomechanical methods; though among each type of assessment, there is no

single operational definition of thrust. Operational definitions used in various studies, along with prevalence and reliability estimates, are presented in **Table 1.2**. These different operational definitions are, in part, responsible for varying estimates of thrust prevalence across different studies (Sosdian et al., 2016)<sup>1</sup>. Visual and quantitative methods of assessing thrust each have specific strengths and limitations. Visual assessment of thrust can be easily employed in a clinic setting where expensive gait laboratory equipment is unavailable; in other words, it is a simple and inexpensive method for clinicians to detect potential increased loads at the knee. While visual observation of knee thrust has shown good inter- and intra-rater reliability (Chang et al., 2004; Fukutani et al., 2016), it is inherently limited by its non-quantitative nature. Quantitative assessment of thrust allows for accurate estimation of joint loads and calculation of joint angles and angular velocity, and therefore is useful for not only assessing thrust, but also testing clinical interventions for thrust and the reduction of knee loads. Nevertheless, quantitative methods require burdensome and expensive equipment that is not readily available in all clinical settings. Further, the ability of biomechanical equipment to detect slight acceleration or changes in joint angles that are invisible to the naked eye may lead researchers to over-estimate the prevalence of knee thrust (e.g., Sosdian et al., 2016; Yoshimura et al., 2002).

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<sup>1</sup> Other factors responsible for differing thrust prevalence across studies include participant demographic characteristics, such as sex and body mass index (BMI) (Fukutani et al., 2016).

**Table 1.2.** Review of biomechanical and visual methods for assessment of varus thrust.

Study	Definition	Thrust Prevalence	Reliability
<b>Biomechanical Assessment of Varus Thrust</b>			
<b>Yoshimura et al. (2002)</b>	The first acceleration peak after the heel strike arising in a lateral direction followed by a second peak in the medial direction.	79.1% (91/115)	Not reported
<b>Hunt et al. (2011)</b>	A definitive increase or peak in knee adduction angle during mid-stance, as opposed to a constant knee adduction angle throughout mid-stance.	N/A - Single-subject study	N/A - Single-subject study
<b>Kuroyanagi et al. (2012)</b>	The differences in marker HKA angles (based on markers on the greater trochanter, lateral joint line of the knee, and lateral malleolus) between heel strike and the first varus peak in initial (32.3% ± 9.9%) stance.	Not reported	Root mean square error = 0.35°
<b>Mahmoudian et al. (2016)</b>	The difference between the knee adduction angle at heel strike and the first maximum adduction angle during the stance phase of gait; designated “present” if this difference > 2.02°.	Not reported	Not reported

**Table 1.2.** Review of biomechanical and visual methods for assessment of varus thrust.

<b>Study</b>	<b>Definition</b>	<b>Thrust Prevalence</b>	<b>Reliability</b>
<b>Sosdian et al. (2016)</b>	The largest, most abrupt (determined using the peak knee angular velocity), frontal plane movement in either the varus or valgus direction during the loading phase (the first 30% of stance phase). Any magnitude above 0 degrees was eligible to be defined as a thrust.	57% (48/84)  (66% in OA cohort, 48% in asymptomatic controls)	Not reported
<b>Shimada et al., (2016)</b>	The varus-valgus angular displacement found by subtracting minimal varus from maximal varus during the loading response phase defined as the first 10% of the gait cycle.	Not reported	Not reported
<b>Visual Assessment of Varus Thrust</b>			
<b>Chang et al. (2004, 2010)</b>	Dynamic worsening or abrupt onset of varus alignment as the limb accepted weight, with a return to less varus alignment during lift-off and the swing phase of gait.	34.6% (1245/3592)  (36.7% in persons with OA, 32.1% in persons without OA)	Intra-rater $\kappa =$  0.81

**Table 1.2.** Review of biomechanical and visual methods for assessment of varus thrust.

Study	Definition	Thrust Prevalence	Reliability
<b>Lo et al. (2012)</b>	First appearance of varus or abrupt worsening of existing varus while the limb is bearing weight during ambulation, with a return of the limb to a less varus alignment during the swing or non-weight-bearing phase of gait.	30.5% (25/82)	Inter-rater $\kappa =$ 0.75 (reported by Bennell et al., 2015)
<b>Fukutani et al. (2016)</b>	Criteria were as follows: 1) movement of knee joint on the frontal plane; 2) motion from initial contact to mid-stance of the stance phase; 3) lateral movement of the tibial tuberosity relative to hip and ankle joint, independent from hip external rotation plus knee flexion, with a resultant increase in varus alignment; and 4) return to a more neutral position at unloading.	16.2% (46/284)	Intra-rater $\kappa =$ 0.81, 0.92 Inter-rater $\kappa =$ 0.73

## **Interventions Targeting Medial Knee Loads and Varus Thrust**

Literature on interventions that specifically target knee thrust is limited, as most interventions are directed towards reducing medial knee loads and the KAM (e.g., Barrios et al., 2010; Fregly et al., 2009; Pollo et al., 2002; Schache et al., 2008; Shull et al., 2013; Simic et al., 2011). Surgical and non-surgical interventions relating to knee thrust are described below.

### *Surgical*

High tibial osteotomy is a common treatment in younger patients with varus knee malalignment and symptomatic medial tibiofemoral OA. Restoration of normal tibiofemoral alignment through high tibial osteotomy has been recommended in order to correct varus thrust (Naudie et al., 2004; Noyes et al., 2000). Total knee arthroplasty was also reported to decrease the magnitude of lateral (varus) thrust to a level of statistical significance by six months post-operation, and this magnitude continued to decrease at one year post-operation (Shimada et al., 2016).

### *Non-Surgical*

Because surgical approaches to reduce varus thrust and medial knee loads are costly and invasive, the development of non-surgical techniques is of great interest. These techniques can include gait modification and neuromuscular retraining. In a study of 50 knees with medial OA, Ogata et al. (1997) found that a valgus (lateral-wedge) insole reduced the lateral peak in acceleration associated with varus thrust (i.e., the amplitude of thrust) by 23.7% ( $\pm$  16.5%). Over half of the knees in this study showed clinical

improvement, defined as a reduction in pain, within a week of implementation, though no clinical improvement was seen in knees with more severe OA.

In a single-subject study, Hunt et al. (2011) employed four gait modification strategies (toe out, trunk lean, orthotics, lateral wedges) aimed at minimizing the magnitude of varus thrust. Varus thrust was still evident across all modifications, though the peak knee adduction angle was reduced by 38% with increased trunk lean.

Bennell et al. (2015) found that persons with varus thrust had a larger reduction in pain following a neuromuscular exercise regime (compared to a quadriceps strengthening regime). The authors hypothesized that neuromuscular exercise reduced thrust, which was related to pain, but this study did not assess whether the occurrence or magnitude of thrust was reduced following this intervention.

### **Significance and Specific Aims**

Because varus thrust can be observed visually and is potentially modifiable using non-invasive bracing or gait retraining interventions, it presents an opportunity for non-surgical preventative intervention for knee OA and other painful knee and lower extremity symptoms. While the consequences of varus thrust for medial knee OA progression and prevalent knee pain have been described, the extent to which thrust affects the risk of painful injury to neighboring joints has not been previously studied. Additionally, it is not currently understood what factors, whether structural or sensorimotor, contribute to the occurrence of thrust.

The objective of this study is to identify the possible causes and consequences of varus thrust by way of a longitudinal investigation of knee thrust as a risk factor for knee

structural damage and painful injury to other lower limb joints, and a cross-sectional investigation of the anatomical and sensorimotor correlates of thrust.

The first two aims of this study will build on and enhance what is known from previous studies of varus knee thrust as a risk factor for structural (Aim 1, Chapter 2) and symptomatic (Aim 2, Chapter 3) change to the knee joint. The latter two aims of this research will expand the study of varus knee thrust beyond its role as a risk factor for knee injury: Aim 3 (Chapter 4) will examine knee thrust as a biomechanical event along the kinematic chain of the lower limb and its role in the development of painful symptoms to neighboring joints, and Aim 4 (Chapter 5) will analyze anatomical and sensorimotor conditions that could contribute to increased thrust prevalence in at-risk older adults.

The central hypothesis of this study is that varus thrust is a potent risk factor for structural damage and painful symptoms at the knee as well as for painful injury to the hip and ankle, and that varus thrust is most common in knees with potentially-modifiable sensorimotor or structural impairments. We test this hypothesis with the following specific aims:

**Aim 1.** Determine the relation of varus knee thrust observed during walking to MRI-detected incident and worsening medial knee cartilage damage and BMLs in older adults with or at risk for knee OA. *Hypothesis 1:* knees with varus thrust have higher odds of incident and worsening cartilage lesions compared to knees without thrust.

**Aim 2.** Determine the longitudinal effects of varus knee thrust on incident and worsening knee pain over two years in older adults with or at risk for OA. *Hypothesis 2:* knees with

thrust have a greater risk of incident and worsening WOMAC knee pain compared to knees without thrust.

**Aim 3.** Determine the effects of thrust on the entire lower limb through a quantitative analysis of thrust and an epidemiological study of associated risk for pain in lower limb joints in older adults with or at risk for knee OA.

**3.1.** Assess differences in frontal-plane joint angles and joint moments in the lower extremity between the affected and unaffected limbs in a single OA subject with varus knee thrust in one limb. This is a hypothesis-generating study to provide rationale for further study of biomechanical alterations proximal and distal to the knee in larger samples of varus thrust patients.

**3.2.** Determine the relationship of varus knee thrust to the incidence of frequent low back, hip, ankle, and foot pain in older adults with or at risk for OA. *Hypothesis 3.2:* knees with thrust have higher odds of incident frequent pain at neighboring lower extremity joints compared to knees without thrust.

**Aim 4.** Evaluate the cross-sectional relationship between structural and sensorimotor impairments and the presence of varus knee thrust in older adults with or at risk for knee OA. *Hypothesis 4:* knee thrust is most prevalent in persons with more severe anatomical/structural impairments (e.g., knee joint laxity and malalignment) and in individuals with more severe sensorimotor impairments (e.g., muscle weakness and diminished vibration and joint position sense) compared to those without such impairments. Overall, sensorimotor impairments are more strongly associated with the presence of thrust than are structural impairments.

## **General Methods**

This work leverages data on varus knee thrust collected from participants in the Multicenter Osteoarthritis (MOST) Study.

### *Study Sample*

The MOST study is a prospective, observational cohort study funded by the National Institute on Aging. The overall aims of MOST are to identify novel and modifiable risk factors for radiographic and symptomatic knee OA and to determine whether risk factors for new disease differ from those for worsening disease (Segal et al., 2013). MOST consists of community-sampled older adults either with preexisting knee OA or with an increased risk of developing it. Factors considered to contribute to an increased risk of knee OA included being overweight; having knee symptoms without radiographic OA; and having a prior knee injury or previous knee surgery. At baseline, MOST recruited 3026 men and women (ages 50-79) from the general population surrounding Iowa City, Iowa, and Birmingham, Alabama. The MOST protocol was approved by the Institutional Review Boards at the University of Iowa; University of Alabama, Birmingham; University of California, San Francisco; and Boston University. Details of the MOST sample, including exclusion criteria, are described elsewhere (Segal et al., 2013).

Following the baseline visit, data was collected from MOST participants at 15-, 30-, 60-, and 84-month clinic visits, and a telephone interview at 72 months. Data collected through the MOST study included (but was not limited to) knee imaging, pain

and proprioception data, physical performance and body composition data, self-reported health data, sensory modality data, and muscle strength data.

Gait data were collected from eligible participants who completed the MOST 60-month clinic visit. During the gait exam, participants dressed in short pants and their customary shoes were instructed to walk across a 4.9-meter pressure-sensitive gait carpet, during repeated trials at a self-selected normal pace. A high-speed (60 Hz) video camera positioned at a fixed distance from the end of the walkway recorded each subject's gait pattern<sup>2</sup>. The camera was mounted to the wall and its position relative to the walkway was standardized at both clinic sites. GAITRite resident software (GAITRite Inc., Clifton, NJ, <http://www.gaitrite.com>) was used to compute spatiotemporal gait parameters such as walking velocity and step length.

MOST participants in the 60-month gait exam had to be able to walk independently over short indoor distances without the use of a walking aid or orthotic knee brace. Participants with recent (< 6 weeks) lower limb injury resulting in restricted weight bearing for over one week, recent hospitalization for a cardiovascular or respiratory disorder, lower limb amputation proximal to the toes, or difficulty walking because of a neurological condition were excluded.

#### *Assessment of varus knee thrust*

A single trained observer (AW), blinded to knee disease status, assessed thrust from high-speed videos of participants in the MOST 60-month gait exam during two self-

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<sup>2</sup> It should be noted that the original intention of the video recording was not for the assessment of varus thrust; this may explain differences in observer error rates between this and other studies with a similar thrust assessment protocol (e.g., Fukutani et al., 2015).

paced walking trials. Skin markers were placed over the centers of the patellae and tibial tuberosities to facilitate visualization of the knee. Knees were excluded from the thrust assessment if a clear view of either marker was obscured by clothing. The observer created a protocol for the assessment of thrust from these videos following the definition of varus thrust reported by Chang et al. (2010), specifically, the dynamic worsening or abrupt onset of varus alignment during the weight acceptance phase of gait, with a return to more neutral alignment during the lift-off and swing phases. Thrust presence was graded on a Likert-type scale of “definitely present,” “probably present,” “probably absent,” or “definitely absent” using observer-created operational definitions (**Table 1.3**).

**Table 1.3.** Scoring system and operational definitions for visual assessment of knee thrust from high-speed videos in the MOST study.

<b>Score</b>	<b>Label</b>	<b>Operational Definition</b>
0	“Thrust Definitely Absent”	No observable frontal plane motion.
1	“Thrust Probably Absent”	Slight frontal plane motion without visible change in alignment, possible rotation (transverse plane motion) present. The absence of thrust cannot be determined with confidence.
2	“Thrust Possibly Present”	Frontal plane motion is visible, but without a distinct change in alignment. The presence of thrust cannot be determined with confidence.
3	“Thrust Definitely Present”	Frontal plane motion with a distinct and unmistakable change in alignment is present.

If a knee was graded as having thrust “definitely present” or “probably present,” the proportion of steps exhibiting definite or probable thrust was noted as thrust during “all steps,” “greater than half (but not all) of steps,” or “fewer than half of steps.” For the purposes of the current study, a simplified dichotomous variable was defined, wherein thrust was considered present when thrust was graded “definitely present” during any ( $\geq$  1) steps or “probably present” during “all steps.” We tested the thrust assessment protocol for intra-rater reliability using an unweighted kappa analysis. A reliability sample of 30 knees is sufficient for a desired kappa of 0.6 at 90% power (Sim and Wright, 2005); however, as thrust is an infrequent trait, we increased the sample to 150 knees, enriched with a proportion of knees with static varus malalignment (a potential correlate of thrust) and balanced between the two clinic sites. This randomly-selected subsample underwent blinded reassessment, revealing substantial intra-rater reliability for the dichotomous variable of varus thrust ( $\kappa = 0.73$ ; 95% CI 0.63, 0.84).

## CHAPTER 2.

### **VARUS THRUST DURING WALKING AND THE RISK OF INCIDENT AND WORSENING MEDIAL TIBIOFEMORAL MRI LESIONS: THE MULTICENTER OSTEOARTHRITIS STUDY**

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-Study conception and design: Wink, Gross, Felson.

-Acquisition of data: Wink, Guermazi, Roemer, Torner, Lewis, Nevitt, Tolstykh, Felson.

-Analysis and Interpretation of data: All authors.

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## **ABSTRACT**

*Objective.* To determine the association of varus thrust during walking to incident and worsening medial tibiofemoral cartilage damage and bone marrow lesions (BMLs) over two years in older adults with or at risk for OA.

*Method.* Subjects from the Multicenter Osteoarthritis Study were studied. Varus thrust was visually assessed from high-speed videos of forward walking trials. Baseline and two-year MRIs were acquired from one knee per subject and read for cartilage loss and BMLs. Logistic regression with generalized estimating equations was used to estimate the odds of incident and worsening cartilage loss and BMLs, adjusting for age, sex, race, body mass index, and clinic site. The analysis was repeated stratified by varus, neutral, and valgus alignment.

*Results.* 1007 participants contributed one knee each. Varus thrust was observed in 29.9% of knees. Knees with thrust had 2.17 [95% CI: 1.51, 3.11] times the odds of incident medial BML, 2.51 [1.85, 3.40] times the odds of worsening medial BML, and 1.85 [1.35, 2.55] times the odds of worsening medial cartilage loss. When stratified by alignment, varus knees also had significantly increased odds of these outcomes.

*Conclusion.* Varus thrust observed during walking is associated with increased odds of incident and worsening medial BMLs and worsening medial cartilage loss. Increased odds of these outcomes persist in varus-aligned knees.

## INTRODUCTION

The medial compartment of the tibiofemoral joint is the most commonly affected area in knee osteoarthritis (OA). Potentially-modifiable risk factors for medial knee OA are related to increased or abnormal loads to the medial joint compartment. One such risk factor is varus knee thrust, a visible manifestation of excessive varus frontal-plane tibiofemoral motion during the weight-acceptance phase of gait with a return to neutral or less varus alignment in the late-stance phase (Chang et al., 2010). As thrust is potentially modifiable by non-invasive methods such as bracing, muscle strengthening, and gait retraining (Hunt et al., 2011), its relation to OA-related structural damage is of interest. Varus thrust has been associated with a four-fold increase in the odds of medial radiographic OA disease progression (Chang et al., 2004). Knees with varus thrust have also been reported to be at least four times more likely to have pain during weight-bearing than those without a varus thrust (Lo et al., 2012).

To date, the relationship of knee thrust to OA risk has only been assessed through radiography (Chang et al., 2004, 2010). Radiographic osteophytes and joint space narrowing are likely to provide only a coarse measure of the structural damage sustained in the presence of knee thrust. Magnetic resonance imaging (MRI) is a more sensitive measure of structural damage: cartilage damage can be directly visualized on MRI and damage to the bone can also be ascertained through examination of bone marrow lesions (BMLs), which represent traumatic lesions to subcortical bone. These lesions can appear prior to the development of features characteristic of radiographic OA (Guermazi et al.,

2012; Sharma et al., 2015), and therefore detecting these lesions presents an opportunity for early detection and prevention of knee OA.

Varus thrust represents a dynamic malalignment of the knee. Cartilage damage and BML have been previously shown to increase in both frequency and size in response to altered static knee alignment (Felson et al., 2003; Hunter et al., 2006; Sharma et al., 2008; Hayashi et al., 2012). Varus thrust has also been associated with the external knee adduction moment (KAM), an indicator of medial tibiofemoral load derived from gait analysis (Chang et al., 2004). Prior studies have shown an association between the KAM and the presence of medial BML (Bennell et al., 2010; Chang et al., 2015) and cartilage loss (Creaby et al., 2010; Bennell et al., 2011; Chang et al., 2015). It is therefore likely that varus thrust will have a similar effect on the development of these lesions. Unlike static alignment or the KAM, thrust can be assessed without the aid of radiographic or gait laboratory equipment; therefore detecting an association between thrust and MRI lesions justifies the use of thrust assessment as an inexpensive alternative to other methods of assessing OA risk.

Our objective was to determine the relation of varus knee thrust observed during walking to MRI-detected incident and worsening medial knee cartilage damage and BMLs in older adults with or at risk for knee OA. We hypothesized that knees with thrust would have higher odds of those outcomes compared to knees without thrust.

## **METHODS**

### *Sample*

The Multicenter Osteoarthritis Study (MOST) is a prospective, observational cohort study of knee OA in older Americans that have OA or are at an increased risk of developing it. Factors considered to contribute to an increased risk of knee OA included being overweight; having knee symptoms without radiographic OA; and having a prior knee injury or previous knee surgery. Subjects were recruited from two communities: Birmingham, Alabama, and Iowa City, Iowa. The MOST protocol was approved by the Institutional Review Boards at the University of Iowa; University of Alabama, Birmingham; University of California, San Francisco; and Boston University. Details of the MOST sample, including exclusion criteria, are described elsewhere (Segal et al., 2013).

Gait data were collected from eligible participants who completed the MOST 60-month clinic visit. Participants were instructed to walk across a 4.9-meter pressure-sensitive gait carpet, during repeated trials at a self-selected normal pace. A high-speed (60 Hz) video camera positioned at a fixed distance from the end of the walkway recorded each subject's gait pattern. The camera was mounted to the wall and its position relative to the walkway was standardized at both clinic sites. GAITRite resident software (GAITRite Inc., Clifton, NJ, <http://www.gaitrite.com>) was used to compute spatiotemporal gait parameters such as walking velocity and step length.

MOST participants in the 60-month gait exam had to be able to walk independently over short indoor distances without the use of a walking aid or orthotic

knee brace. Participants with recent (< 6 weeks) lower limb injury resulting in restricted weight bearing for over one week, recent hospitalization for a cardiovascular or respiratory disorder, lower limb amputation proximal to the toes, or difficulty walking because of a neurological condition were excluded.

#### *Assessment of varus knee thrust*

A single trained observer (AW), blinded to knee disease and MRI status, assessed thrust from high-speed videos of participants in the MOST 60-month gait exam during two self-paced walking trials. Participants dressed in short pants and their customary shoes. Skin markers were placed over the centers of the patellae and tibial tuberosities to facilitate visualization of the knee. Knees were excluded from the thrust assessment if a clear view of either marker was obscured by clothing. Thrust was defined as the dynamic worsening or abrupt onset of varus alignment during the weight acceptance phase of gait, with a return to more neutral alignment during the lift-off and swing phases (Chang et al., 2010) (**Figure 2.1**). Thrust presence was graded on a Likert-type scale of “definitely present,” “probably present,” “probably absent,” or “definitely absent.” Further, for knees with thrust “definitely present” or “probably present,” the proportion of steps exhibiting definite or probable thrust was noted as thrust during “all steps,” “greater than half (but not all) of steps,” or “fewer than half of steps.” For the purposes of the current study, a simplified dichotomous variable was defined, wherein thrust was considered present when thrust was graded “definitely present” during any ( $\geq 1$ ) steps or “probably present” during “all steps.” A randomly-selected subsample of 150 knees (with balanced representation of the two clinic sites) underwent blinded reassessment, revealing

substantial intra-rater reliability for the dichotomous variable of varus thrust ( $\kappa = 0.73$ ; 95% CI 0.63, 0.84).



**Figure 2.1.** Assessment of varus thrust from high-speed video. The subject's left knee is in a neutral position during early stance (A), abruptly thrusts into varus during mid-stance (B), and then returns to neutral during late stance (C). Dotted lines are for illustrative purposes only and do not represent actual joint angles.

### *MRI acquisition*

Subjects in the MOST Study underwent MRI of bilateral knees with a 1.0T extremity magnetic resonance system (OrthOne; ONI Medical Systems, Wilmington, MA) at 60 and 84 months. All MRIs were acquired using fat suppressed, fast spin-echo, proton density-weighted sequences in the sagittal plane (repetition time [TR] 4800 ms, time to echo [TE] 35 ms, slice thickness 3 mm, interslice gap 0 mm, field of view [FOV] 14 cm  $\times$  14 cm, matrix 288  $\times$  192 pixels, number of excitations [NEX] 2) and the axial plane (TR 4700 ms, TE 13.2 ms, slice thickness 3 mm, interslice gap 0 mm, FOV 14 cm  $\times$  14 cm, matrix 288  $\times$  192 pixels, NEX 2) and a short-tau inversion recovery (STIR) sequence in the coronal plane (TR 7820 ms, TE 14 ms, inversion time 100 ms, slice

thickness 3 mm, interslice gap 0 mm, FOV 14 cm × 14 cm, matrix 256 × 256 pixels, NEX 2) (Javaid et al., 2010).

#### *Assessment of cartilage loss and BMLs*

To assess cartilage loss, two musculoskeletal radiologists (AG and FWR) with 15 and 13 years of experience in semiquantitative MRI analysis, respectively, scored one knee per subject using the Whole-Organ MRI Score (WORMS) for knee OA (Peterfy et al., 2004). Where high quality MR images were available from both the 60 and 84 month exams for both knees of a subject, the one knee to be read was selected at random. Inter-reader weighted kappa values for WORMS scoring ranged from 0.62 (95% CI 0.57, 0.68) for BML to 0.78 (95% CI 0.76, 0.81) for cartilage (Javaid et al., 2010). For each knee, five medial tibiofemoral sub-regions were scored. We assessed incident cartilage loss for sub-regions with a WORMS score of 0 (normal thickness) or 1 (normal thickness but increased signal) at baseline, and defined incident cartilage damage as a WORMS score  $\geq$  2 at two years. Worsening cartilage damage was defined as any increase in WORMS score over two years, including incidence and within-grade worsening. Sub-regions were excluded from analysis if they had the maximum WORMS score at 60 months, as there could theoretically be no progression. To investigate more definitive changes in cartilage damage, we repeated this analysis using a stricter definition of progression: a full-grade or greater increase in WORMS score.

Subchondral BMLs were scored from 0-3 based on the extent of involvement for each of five medial tibiofemoral sub-regions (0 = none; 1  $\leq$  25% of the sub-region; 2 = 25-50%; 3  $\geq$  50%). A within-grade change of BML was also recorded, which designated definite change that did not fulfil criteria for a full-grade change in BML score (Roemer et al., 2012). For sub-regions with a score of 0 at baseline, BML incidence was defined as an increase in score over two years. Among knees with a sub-maximal BML score at 60 months, BML enlargement (worsening) was defined as any increase in score over two years, including incidence.

#### *Assessment of static knee alignment*

Mechanical hip-knee-ankle (HKA) alignment was assessed at the MOST 60-month visit from full-view, fully-extended, weight-bearing anterior-posterior radiographs of the lower extremity. The HKA angle was defined as the angle formed by the intersection of a line from the center of the head of a femur to the center of the tibial spines and a second line from the center of the talus to the center of the tibial spines. Varus alignment was defined as a mechanical HKA angle less than 179 degrees; knees with HKA angles between 179 and 181 degrees were considered neutral; and knees with HKA angles greater than 181 degrees were considered valgus.

#### *Statistical analysis*

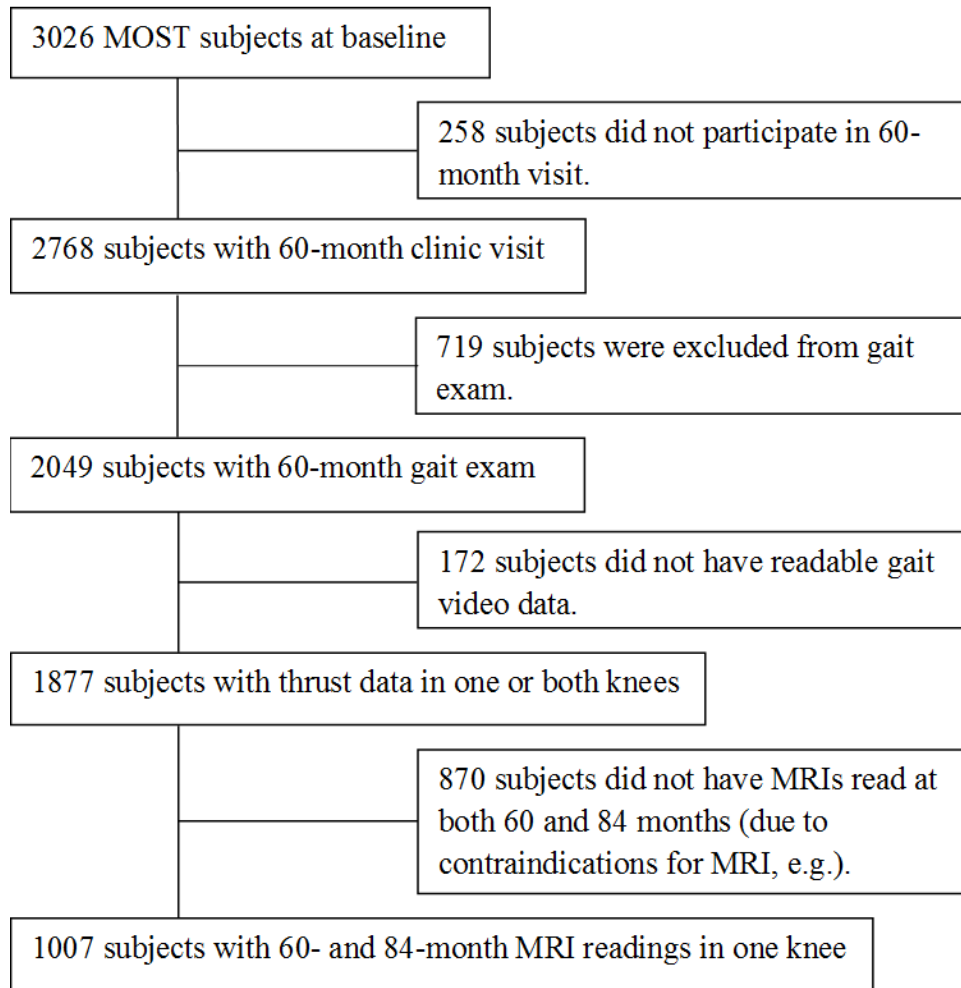
We evaluated the odds of incident and worsening tibiofemoral joint damage (i.e., cartilage loss and BML) in the presence of varus thrust using logistic regression with an adjustment for age, sex, race, body mass index (BMI), and clinic site. Generalized estimating equations were used to account for correlation between multiple sub-regions

within a single knee. In sensitivity analysis to determine the whether the relationship of varus thrust to risk of MRI outcomes was modified by the presence of static varus malalignment, the main analysis was repeated separately within varus and non-varus alignment strata, and a multiplicative interaction term was added to the model. Results from each logistic regression model are reported as odds ratios (ORs) with associated 95% confidence intervals (CIs). Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

## RESULTS

Of 2768 participants in the MOST 60-month clinic visit, 2049 met eligibility criteria for completion of the gait exam. Of these, 1007 subjects had readable videos for assessment of knee thrust along with readable MRIs at 60-month (baseline) and 84-month follow-up visits. These 1007 subjects contributed one knee each (**Figure 2.2**), with a total of 5035 knee sub-regions available for the sub-region-based analysis. At baseline, 85 sub-regions had maximal WORMS scores for cartilage damage while 44 sub-regions had maximal scores for BML; these sub-regions were excluded from analyses of worsening damage. Varus thrust was observed in 29.9% of eligible knees. Of the 301 knees with thrust, 161 (53.5%) were graded as thrust “definitely present on any steps” and 140 (46.5%) were graded as thrust “probably present on all steps.” Characteristics of the study sample are presented in **Table 2.1**. Subjects with varus thrust were slightly older than subjects without thrust ( $p = 0.046$ ), and the proportion of males to females was higher in the group with thrust than in the group without thrust ( $p < 0.0001$ ). A larger proportion of knees with thrust had radiographic tibiofemoral OA (defined as Kellgren-

Lawrence grade  $\geq 2$ ) compared to knees without thrust ( $p = 0.0007$ ), and the mean HKA angle in knees with thrust was more varus than in knees without thrust ( $p < 0.0001$ ).



**Figure 2.2.** Study subject selection flowchart.

**Table 2.1.** Demographics of study participants (n = 1007 subjects contributing 1 knee each).

	<b>With Varus Thrust (n = 301)</b>	<b>Without Varus Thrust (n = 706)</b>
<b>Age, years</b> (mean $\pm$ S.D.)	67.4 $\pm$ 7.6	66.4 $\pm$ 7.5
<b>Sex</b> (% Female)	49.8	67.8
<b>Racial Background</b>		
-White/Caucasian (%)	93.7	90.9
-Black/African American (%)	5.3	8.1
-Other (%)	1.0	1.0
<b>BMI, kg/m<sup>2</sup></b> (mean $\pm$ S.D.)	29.8 $\pm$ 4.9	29.3 $\pm$ 4.7
<b>Site</b> (% Alabama)	32.7	41.2
<b>Radiographic Tibiofemoral OA*</b> (%)	45.5	34.2
-KL = 2 (%)	16.6	18.8
-KL = 3 (%)	22.9	14.5
-KL = 4 (%)	6.0	1.0
<b>Hip-Knee-Ankle Angle, degrees</b> (mean $\pm$ S.D.)	177.5 $\pm$ 3.2	179.0 $\pm$ 3.0

\*Defined as Kellgren-Lawrence (KL) grade  $\geq$  2

As shown in **Table 2.2**, knees with varus thrust had 2.17 times the odds of medial compartment BML incidence at two years (95% CI: 1.51, 3.11) after adjusting for covariates. However, there was no statistically significant association between varus thrust and incident medial cartilage damage. Knees with varus thrust had 2.51 times the odds of medial BML worsening (95% CI: 1.85, 3.40) and 1.85 times the odds of worsening medial cartilage damage (95% CI: 1.35, 2.55) after adjusting for covariates. Further adjustment for baseline Kellgren-Lawrence grade attenuated these results somewhat, but did not alter either their direction or statistical significance. Results were similar when a stricter definition of worsening (at least a full grade WOMBS increase) was applied (results not shown).

**Table 2.2.** Odds of incident and worsening MRI lesions in the presence of varus knee thrust.

<b>Outcome</b>	<b>n / N*</b>	<b>Crude OR (95% CI)</b>	<b>P</b>	<b>Adjusted OR<sup>†</sup> (95% CI)</b>	<b>P</b>	<b>Adjusted OR<sup>††</sup> (95% CI)</b>	<b>P</b>
<b>Incident Medial BML</b>	173 / 4399	<b>2.10 (1.48, 2.97)</b>	<b>&lt;0.0001</b>	<b>2.17 (1.51, 3.11)</b>	<b>&lt;0.0001</b>	<b>2.01 (1.42, 2.84)</b>	<b>&lt;0.0001</b>
<b>Incident Medial Cartilage Loss</b>	118 / 3395	0.78 (0.47, 1.30)	0.35	0.77 (0.45, 1.29)	0.32	0.75 (0.45, 1.26)	0.28
<b>Worsening Medial BML</b>	346 / 4987	<b>2.43 (1.82, 3.24)</b>	<b>&lt;0.0001</b>	<b>2.51 (1.85, 3.40)</b>	<b>&lt;0.0001</b>	<b>2.01 (1.52, 2.66)</b>	<b>&lt;0.0001</b>
<b>Worsening Medial Cartilage Loss</b>	379 / 4950	<b>1.77 (1.30, 2.41)</b>	<b>0.0003</b>	<b>1.85 (1.35, 2.55)</b>	<b>0.0002</b>	<b>1.60 (1.17, 2.19)</b>	<b>0.003</b>

\*Sub-regions with outcome / total number of sub-regions analyzed

<sup>†</sup>Adjusted for age, sex, race, BMI, and clinic site

<sup>††</sup>Adjusted for age, sex, race, BMI, clinic site, and *baseline KL grade*

To determine whether the relationship between thrust and MRI outcomes was modified in the presence of static varus alignment, we repeated each of the main analyses within separate strata of varus and non-varus HKA alignment and introduced an interaction term into our multivariable regression model. Of 1007 knees, 576 were varus aligned, and 431 were non-varus (236 were neutral and 195 were valgus). After adjusting for covariates, we found statistically-significant increased odds of incident medial BMLs (OR 2.62; 95% CI: 1.67, 4.10), worsening medial BMLs (OR 2.44; 95% CI: 1.74, 3.42) and worsening medial cartilage loss (OR 1.89; 95% CI: 1.30, 2.75) in varus knees with thrust compared to varus knees without thrust. Among non-varus knees, however, while relationships were in a similar direction, point estimates of the increased odds associated with thrust were of a smaller magnitude and failed to achieve statistical significance (see **Table 2.3**). When examined separately, neutral- and valgus-aligned knees showed no significant relationships with these MRI outcomes (results not shown). The interaction test results were not statistically significant for incident medial cartilage loss ( $p = 0.87$ ), worsening medial BML ( $p = 0.12$ ), and worsening medial cartilage loss ( $p = 0.40$ ), though the results neared significance for incident medial BML ( $p = 0.07$ ).

**Table 2.3.** Adjusted odds of incident and worsening MRI lesions in the presence of varus knee thrust in varus and non-varus knees with a test for interaction.

Outcome	Varus Knees (HKA < 179°) with Varus Thrust			Non-Varus Knees (HKA ≥ 179°) with Varus Thrust			Test for Interaction
	n / N*	OR <sup>†</sup> (95% CI)	p	n / N	OR <sup>†</sup> (95% CI)	p	
<b>Incident Medial BML</b>	108 / 2232	<b>2.62</b> <b>(1.67, 4.10)</b>	<b>0.0001</b>	62 / 2021	1.33 (0.73, 2.40)	0.35	p = 0.07
<b>Incident Medial Cartilage Loss</b>	50 / 1584	0.82 (0.39, 1.72)	0.60	63 / 1695	0.76 (0.36, 1.59)	0.46	p = 0.87
<b>Worsening Medial BML</b>	248 / 2664	<b>2.44</b> <b>(1.74, 3.42)</b>	<b>0.0001</b>	89 / 2148	1.42 (0.77, 2.60)	0.26	p = 0.12
<b>Worsening Medial Cartilage Loss</b>	222 / 2628	<b>1.89</b> <b>(1.30, 2.75)</b>	<b>0.0008</b>	140 / 2149	1.40 (0.75, 2.61)	0.29	p = 0.40

\*Sub-regions with outcome / total number of sub-regions analyzed

†Adjusted for age, sex, race, BMI, and clinic site

## **DISCUSSION**

Varus knee thrust presence visualized during walking was associated with increased odds of incident and worsening BMLs and with increased odds of worsening cartilage damage after adjusting for age, sex, race, BMI, and clinic site. There was no statistically significant association found between varus thrust and incident cartilage damage. It is important to note that the assessment of thrust and our definition of “baseline” took place 60 months (5 years) into the MOST study, and therefore these results are perhaps evidence of a “depletion-of-susceptibles” effect, wherein knee sub-regions that had not developed cartilage damage by that point in the MOST study were perhaps not likely to develop it at all. This same effect would have had less influence on results pertaining to the risk that existing damage might worsen in the presence of thrust.

In sensitivity analysis, we found that varus-aligned knees with thrust had increased odds of incident and worsening BML and worsening cartilage damage compared to varus-aligned knees without thrust. In contrast, the effect of thrust on risk of these outcomes was not statistically significant among non varus-aligned knees. These results are similar to the findings of Chang et al. (2004) who saw a three-fold increase in the odds of radiographic OA progression in varus-aligned knees with varus thrust compared to varus-aligned knees without thrust. Furthermore, Lo et al. (2012) and Iijima et al. (2015) reported that varus thrust was more strongly correlated with knee pain than was static varus malalignment alone. Considered together, these findings suggest that dynamic malalignment (i.e., thrust) has potential to compound the trauma placed on the tibiofemoral joint by static malalignment. Unfortunately, our test for statistical interaction

may have been under-powered (evident by wide confidence intervals in the stratified analysis compared to the main analysis), and we could not confirm that the effects of varus thrust on risk of structural damage are modified by the presence of static knee malalignment.

Previous authors have found significant associations between varus knee thrust and knee pain (Lo et al., 2012; Iijima et al., 2015). Our findings of an association between thrust and incident and worsening BMLs suggest a potential mechanism for the relation of thrust to knee pain. BMLs are correlated with knee pain in OA (Felson et al., 2001; 2007), and BMLs are hypothesized to be the source of this pain due to the presence of nociceptive fibers in the bone marrow. Bone marrow lesions are thought to be the result of ongoing local bone trauma associated with malalignment (Felson et al., 2003; Lo et al., 2005). The repetitive loading created by thrust could cause such an injury and elicit a pain response in bone. Further investigation into the role of thrust in the development of knee pain is required.

Among knees without radiographic OA, Guermazi et al. (2012) found a high prevalence of MRI detected features, and Sharma et al. (2015) found that worsening MRI lesions were associated with incident radiographic OA over three years. In knees with OA, knees with medial BMLs had over six times the odds of medial disease progression compared to knees without BMLs (Felson et al., 2003). The association of thrust with MRI lesions presents an opportunity to identify those without, but at risk for, or at the early stages of radiographic knee OA.

Hunt and Bennell (2011) identified factors correlated with the peak KAM and therefore indicative of increased knee joint loading that could be easily identified in the clinic. These factors included body mass, tibial alignment, and walking speed. Visually-observed varus knee thrust has been shown to be correlated with several quantitatively-derived gait variables including external KAM, peak knee varus angular velocity, and peak knee varus angle during stance (Chang et al., 2004; Hunt et al., 2011; Kuroyanagi et al., 2012; Chang et al., 2013). Visual detection of varus thrust is another reliable alternative to expensive gait analysis to detect increased loading to the medial knee joint.

OA risk factors resulting from increased mechanical loading are potentially modifiable using noninvasive and inexpensive therapies (Fregly et al., 2009). Hunt et al. (2011) employed various gait-related interventions (increased toe-out, ipsilateral trunk lean, custom-made orthotics, and lateral-wedge insoles) known to reduce medial joint load in a single subject with varus thrust. While thrust was still evident following these modifications, the magnitude of the thrust as well as the peak KAM was reduced in response to increased toe-out and trunk lean. Bennell et al. (2015) found that a neuromuscular exercise regime focusing on trunk and lower extremity position and movement quality improved pain and physical function in those with thrust, though thrust during the course of the exercise intervention was not assessed. As an alternative to these methods that require the patient to adopt a new gait pattern or exercise regime, valgus bracing of the knee has also been shown to reduce medial knee loads and the moments of force associated with varus thrust during walking (Pollo et al., 2002). Further research

regarding the specific causes of knee thrust is necessary to better develop strategies to mitigate thrust.

This study's strengths include the large sample size as well as its longitudinal design. Limitations are those inherent to studies relying on visual assessment of gait. While visual assessment of thrust from high-speed videos yielded high intra-rater reliability, conditions in the clinic setting (e.g., lighting, camera angle relative to subject) as well as conditions of MOST participants (e.g., body mass, walking a non-straight path) could have interfered with our ability to accurately detect the presence of varus thrust. Chang et al. (2013) found that thrust was not only related to peak knee varus angle, but also to peak knee varus angular velocity. While the varus position of the knee can be visualized, it is not possible to accurately estimate the varus angle or assess the angular velocity visually. The non-quantitative nature of the thrust assessment also limits our ability to make conclusions about altered joint loading. For these reasons, this method may not be ideal for precise assessment of the effects of thrust-reducing interventions in clinical trials; however, our method for detecting thrust (and subsequent OA risk) is likely similar to what might be employed in a clinic setting where quantitative testing methods are not available. A second limitation is that thrust was assessed by only one observer, and therefore this study lacks inter-rater reliability data. Using a similar protocol to ours, Iijima et al. (2015) reported good inter-rater reliability ( $\kappa = 0.73$ ) for visual assessment of thrust. While we report strong intra-rater reliability, having multiple readers with varying levels of experience would strengthen our findings. A third limitation is that our static alignment subgroup analysis (i.e., test for interaction) may

have been underpowered. To increase power in our analysis, we combined neutral- and valgus-aligned knees into one “non-varus” category; however, it would be of interest to examine the relationships of thrust to MRI outcomes in these separate strata in a larger sample.

In summary, our results indicate that varus thrust is a risk factor for worsening cartilage loss and BMLs, as well as for BML incidence. The odds of these outcomes persist in knees that are already statically-varus aligned, suggesting that interventions to mitigate varus thrust (and subsequent OA risk) should target these individuals.

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**CHAPTER 3.**

**ASSOCIATION OF VARUS KNEE THRUST DURING WALKING TO  
WORSENING AND INCIDENT WOMAC KNEE PAIN: THE MULTICENTER  
OSTEOARTHRITIS STUDY**

## **ABSTRACT**

*Objective.* To investigate the association of varus knee thrust observed during walking to the odds of worsening and incident WOMAC knee pain in older adults with or at risk of osteoarthritis (OA).

*Methods.* This is a longitudinal study of participants in the Multicenter Osteoarthritis Study (MOST). Video recordings of self-paced walking trials of MOST participants were assessed for the presence of varus thrust at baseline. Knee pain during weight-bearing and non-weight bearing activities was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire at baseline and at two years. Logistic regression was used to estimate the odds of worsening and incident WOMAC knee pain over two years, adjusting for age, sex, race, body mass index, clinic site, and walking velocity. The analyses were repeated, stratified by baseline radiographic OA status.

*Results.* 1623 participants contributed 3024 knees. Varus thrust was observed in 31.5% of knees. Knees with varus thrust had 1.43 times (95% CI: 1.20, 1.70) the odds of any worsening total WOMAC pain and 1.32 times (95% CI: 1.10, 1.59) the odds of clinically-important worsening total WOMAC pain compared to knees without thrust. This statistically-significant relationship persisted across all five individual WOMAC activities and regardless of baseline OA status. Knees with thrust also had 1.78 (95% CI: 1.33, 2.39) times the odds of incident total WOMAC pain.

*Conclusion.* Our results indicate that varus thrust is a risk factor for incident and worsening WOMAC knee pain, regardless of baseline OA status. Targeting varus thrust through non-invasive therapies could reduce the risk of knee pain in older adults with or at risk for knee OA.

## **INTRODUCTION**

The prevalence of knee pain in older adults has been estimated at 25% (Peat et al., 2001) and may be increasing (Nguyen et al., 2011). Knee pain is also a predictor of future knee joint replacement in persons with osteoarthritis (OA) (Conaghan et al., 2010). In addition to pharmacologic therapies and walking aids, biomechanical interventions are recommended for the non-surgical management of knee pain as a symptom of OA; however, evidence of the efficacy of biomechanical interventions varies (McAlindon et al., 2014). Identifying modifiable biomechanical risk factors for knee pain related to OA is of interest.

Varus knee thrust is a visible manifestation of excessive varus frontal-plane tibiofemoral moment during the weight-acceptance phase of gait with a return to neutral or less varus alignment in the late-stance phase (Chang et al., 2010). The relation of varus thrust to structural damage at the knee has been fairly well documented. Varus thrust has been previously linked to increased odds of medial radiographic OA disease progression (Chang et al., 2004) as well as increased odds of worsening cartilage damage and incident and worsening bone marrow lesions (Wink et al., 2017). Importantly, knee thrust can be identified visually in a clinical setting and can potentially be modified using inexpensive and non-invasive therapies (Hunt et al., 2011).

Previous studies have shown a cross-sectional association between varus knee thrust and knee pain (Lo et al., 2012; Iijima et al., 2015; Fukutani et al., 2016). Longitudinal data to confirm the directionality of the relationship between thrust and pain and to describe the effect of thrust on both the onset of new pain and worsening of existing pain are lacking. Using data from the Multicenter Osteoarthritis Study (MOST), our objective was to evaluate the relation of varus thrust observed during walking to the two-year incidence and worsening of WOMAC knee pain. We hypothesized that knees exhibiting a varus thrust would have increased odds of WOMAC knee pain compared to knees without thrust due to increased mechanical stress during gait.

## **METHODS**

### *Sample*

The Multicenter Osteoarthritis Study (MOST) is a prospective, observational cohort study of knee OA in older Americans that have OA or are at an increased risk of developing it. Factors considered to contribute to an increased risk of knee OA included being overweight; having knee symptoms without radiographic OA; and having a prior knee injury or previous knee surgery. Subjects were recruited from two communities: Birmingham, Alabama, and Iowa City, Iowa. The MOST protocol was approved by the Institutional Review Boards at the University of Iowa; University of Alabama, Birmingham; University of California, San Francisco; and Boston University. Details of the MOST sample, including exclusion criteria, are described elsewhere (Segal et al., 2013).

MOST participants in the 60-month gait exam had to be able to walk independently over short indoor distances without the use of a walking aid or orthotic knee brace. Participants with recent (< 6 weeks) lower limb injury resulting in restricted weight bearing for over one week, recent hospitalization for a cardiovascular or respiratory disorder, lower limb amputation proximal to the toes, or difficulty walking because of a neurological condition were excluded.

Gait data were collected from eligible participants who completed the MOST 60-month clinic visit. Participants dressed in short pants and their customary shoes and were instructed to walk across a 4.9-meter pressure-sensitive gait carpet, during repeated trials at a self-selected normal pace. A high-speed (60 Hz) video camera positioned at a fixed distance from the end of the walkway recorded each subject's gait pattern. The camera was mounted to the wall and its position relative to the walkway was standardized at both clinic sites. GAITRite resident software (GAITRite Inc., Clifton, NJ, <http://www.gaitrite.com>) was used to compute spatiotemporal gait parameters such as gait speed.

#### *Assessment of varus knee thrust*

A single trained observer (AW), blinded to knee disease and pain status, assessed thrust from high-speed videos of participants in the MOST 60-month gait exam during two self-paced forward walking trials. Skin markers were placed over the centers of the patellae and tibial tuberosities to facilitate visualization of the knee. Knees were excluded from the thrust assessment if a clear view of either marker was obscured by clothing. Thrust was defined as the dynamic worsening or abrupt onset of varus alignment during

the weight acceptance phase of gait, with a return to more neutral alignment during the lift-off and swing phases (Chang et al., 2010) (**Figure 1**). Thrust presence was graded on a Likert-type scale of “definitely present,” “probably present,” “probably absent,” or “definitely absent.” Further, for knees with thrust “definitely present” or “probably present,” the proportion of steps exhibiting definite or probable thrust was noted as thrust during “all steps,” “at least half (but not all) of steps,” or “fewer than half of steps.” For the purposes of the current study, a simplified dichotomous variable was defined, wherein thrust was considered present when thrust was graded “definitely present” during any ( $\geq 1$ ) steps or “probably present” during “all steps.” A randomly-selected subsample of 150 knees (with balanced representation of the two clinic sites) underwent blinded reassessment, revealing substantial intra-rater reliability for the dichotomous variable of varus thrust ( $\kappa = 0.73$ ).

#### *Assessment of knee pain*

Pain in each knee was evaluated using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Likert 3.1 pain scale at baseline and two years. The WOMAC is a valid and reliable self-report measure of pain and physical function for individuals with knee OA (Jinks et al., 2002). The pain questionnaire consists of five questions related to pain over the past 30 days during weight-bearing (walking, using stairs, standing upright) and non-weight-bearing (in bed, sitting or lying) activities, scored according to severity of pain: 0 (“none”), 1 (“mild”), 2 (“moderate”), 3 (“severe”), or 4 (“extreme”). These individual WOMAC scores (0-4) are summed to obtain the total WOMAC score (maximum of 20). Among knees with submaximal

WOMAC scores at 60 months, worsening pain at 84 months was defined as any increase in WOMAC score. Clinically-important worsening was defined as at least a 20% increase in total WOMAC score for knees with non-zero total WOMAC scores at baseline, and an increase of at least 1.28 in total WOMAC score for knees with a total WOMAC score of 0 at baseline. These criteria for clinically-important worsening are based on definitions reported by Angst et al. (2002) and Tubach et al. (2012).

#### *Assessment of covariates*

Age, sex, and race were self-reported by MOST participants. Clinic site was either Birmingham, Alabama, or Iowa City, Iowa. Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters; weight was measured, following removal of shoes and heavy clothing, using a balance beam scale, and height was measured using a stadiometer. Gait speed was computed during the gait exam, as described above.

#### *Statistical analysis*

In our primary analyses, we assessed the relation of varus thrust observed as present or absent during walking to 1) worsening total WOMAC pain, 2) clinically-important worsening total WOMAC pain, and 3) worsening WOMAC pain across the five individual activity questions. We used logistic regression with generalized estimating equations to account for correlation between two limbs from a subject, adjusting for age, sex, race, BMI, clinic site, and gait speed. We then repeated the main analysis of worsening total WOMAC pain stratified by baseline radiographic OA status (Kellgren-Lawrence (KL) Grade < 2 vs. KL Grade  $\geq$  2). To assess the relation of varus thrust to

incident WOMAC knee pain, we repeated the main analysis on the subset of knees with WOMAC scores of 0 at baseline. Results are reported as odds ratios and 95% confidence intervals (CI); confidence intervals that exclude 1 are considered statistically significant at the 0.05 level. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

## RESULTS

Of 2768 participants in the MOST 60-month clinic visit, 2049 met eligibility criteria for completion of the gait exam. Of these, 1623 participants had readable videos for thrust assessment and completed WOMAC pain questionnaires at the 60- and 84-month clinic visits. These 1623 participants contributed 3024 knees. Demographic characteristics of the study sample are presented in **Table 3.1**. Varus thrust was observed in 31.5% (1010/3024) of knees. At baseline, the mean total WOMAC pain score was 2.40 for all knees; the mean total WOMAC pain scores for knees with and without thrust were 2.57 and 2.32, respectively.

**Table 3.1.** Characteristics of the study sample.

<b>Person-Level Characteristics (n = 1623 participants)</b>	
Age (years, mean $\pm$ SD)	67.3 $\pm$ 7.6
Sex (% Female)	59.9
Race (% White)	88.7
BMI (kg/m <sup>2</sup> , mean $\pm$ SD)	30.4 $\pm$ 5.9
Clinic Site (% Alabama)	41.1
<b>Knee-Level Characteristics (n = 3024 knees)</b>	
Varus Thrust Present (%)	31.5
Baseline Total WOMAC Score (mean $\pm$ SD)	2.40 $\pm$ 2.97
Radiographic Tibiofemoral OA (% K-L $\geq$ 2)	41.0
% K-L = 2	17.4
% K-L = 3	19.0
% K-L = 4	4.6

After adjusting for covariates, knees with a varus thrust had 1.43 times (95% CI: 1.20, 1.70) the odds of any worsening total WOMAC pain and 1.32 times (95% CI: 1.10, 1.59) the odds of clinically-important worsening total WOMAC pain compared to knees without thrust. Knees with varus thrust had statistically-significant increased odds of worsening WOMAC pain across all five individual weight-bearing and non-weight-bearing activity questions (**Table 3.2**). Stratifying by baseline radiographic OA status did not change the direction nor statistical significance of these results: knees with thrust with and without radiographic knee OA at baseline had knees with thrust 1.47 (95% CI 1.13, 1.92) and 1.36 (95% CI 1.03, 1.79) times the odds, respectively, of worsening total WOMAC pain compared to knees without thrust (**Table 3.3**).

To test the association between varus thrust and incident WOMAC knee pain, we examined the subset of 1239 knees that had a total WOMAC pain score of 0 at baseline. Compared to knees without varus thrust, knees with varus thrust had 1.78 (95% CI: 1.33, 2.39) times the odds of incident total WOMAC pain at two years after adjusting for covariates (**Table 3.3**). This statistically-significant positive association persisted regardless of baseline radiographic OA status (results not shown)

**Table 3.2.** Odds of worsening WOMAC pain in the presence of varus thrust.

WOMAC Pain	Varus Thrust Status	n/N*	Adjusted** Odds Ratio (95% C.I.)	p-Value
<b>Total WOMAC Pain Score</b>				
Any Worsening	Present	355/1010	<b>1.43 (1.20, 1.70)</b>	<b>&lt;0.0001</b>
	Absent	625/2194	1.00 (ref)	
Clinically Important Worsening ( $\geq 1.28$ or 20% <sup>†</sup> )	Present	278/1010	<b>1.32 (1.10, 1.59)</b>	<b>0.003</b>
	Absent	500/2194	1.00 (ref)	
<b>Individual WOMAC Pain Questions</b>				
Walking	Present	185/1010	<b>1.29 (1.05, 1.58)</b>	<b>0.02</b>
	Absent	325/2194	1.00 (ref)	
Using Stairs	Present	230/1010	<b>1.37 (1.28, 1.65)</b>	<b>0.001</b>
	Absent	412/2194	1.00 (ref)	
Standing Upright	Present	202/1010	<b>1.41 (1.13, 1.75)</b>	<b>0.002</b>
	Absent	328/2194	1.00 (ref)	
Sitting	Present	163/1010	<b>1.39 (1.11, 1.74)</b>	<b>0.005</b>
	Absent	293/2194	1.00 (ref)	
In Bed	Present	145/1010	<b>1.31 (1.04, 1.64)</b>	<b>0.02</b>
	Absent	268/2194	1.00 (ref)	

\*Number of knees with worsening pain/Total knees

\*\*Adjusted for age, sex, race, BMI, clinic site, and gait speed

<sup>†</sup>Based on the Minimum Clinically Important Difference for WOMAC Pain from Angst et al. (2002); Clinically Important Worsening is an increase of at least 1.28 in WOMAC score for knees with a baseline score of 0 or an increase of at least 20% for knees with WOMAC scores greater than 0.

**Table 3.3.** Subset analyses of thrust and WOMAC knee pain.

<b>Subset</b>	<b>Varus Thrust Status</b>	<b>n/N*</b>	<b>Adjusted** Odds Ratio (95% C.I.)</b>	<b>p-Value</b>
<b>Odds of Worsening Total WOMAC Knee Pain</b>				
Knees without Baseline ROA (KL < 2)	Present	135/447	<b>1.36 (1.04, 1.79)</b>	<b>0.03</b>
	Absent	290/1171	1.00 (ref)	
Knees with Baseline ROA (KL ≥ 2)	Present	171/420	<b>1.47 (1.13, 1.92)</b>	<b>0.005</b>
	Absent	227/703	1.00 (ref)	
<b>Odds of <i>Incident</i> Total WOMAC Knee Pain</b>				
Knees with Baseline WOMAC Scores of 0	Present	122/362	<b>1.78 (1.33, 2.39)</b>	<b>0.0001</b>
	Absent	217/877	1.00 (ref)	

\*Number of knees with outcome/Total knees

\*\*Adjusted for age, sex, race, BMI, clinic site, and gait speed

## **DISCUSSION**

This study investigated the role of varus thrust in the worsening and incidence of WOMAC knee pain after two years. Varus knee thrust observed during walking was associated with increased odds of incident and worsening total WOMAC pain after adjusting for age, sex, race, BMI, clinic site, and gait speed, and independently of baseline knee OA status. Others have suggested that the summed WOMAC score may not be an appropriate assessment of pain (Lo et al., 2012; Stratford et al., 2007); therefore, we examined the five individual WOMAC questions separately and found increased odds of worsening knee pain across all weight-bearing and non-weight-bearing activities.

Lo et al. (2012) first described an association between visually-assessed varus thrust and WOMAC knee pain in a cross-sectional analysis of 82 participants with symptomatic knee OA. Their study showed increased odds of WOMAC knee pain during weight-bearing activities only. Iijima et al. (2015) found a statistically-significant association between varus thrust and knee pain during gait, regardless of varus alignment status, in a cross-sectional study of 266 Japanese patients with medial radiographic knee OA. Fukutani et al. (2016) found a statistically-significant cross-sectional association between varus thrust and pain and stiffness at the knee in a sample of 284 Japanese patients with medial tibiofemoral OA. Our work builds upon these previous studies by demonstrating a longitudinal association between varus thrust and knee pain during both weight-bearing and non-weight-bearing activities in a large cohort of 1623 participants with and without radiographic knee OA.

The results from our individual WOMAC activity analysis (namely, increased odds of worsening WOMAC pain during all weight-bearing and non-weight-bearing activities in the presence of thrust) differ somewhat from the findings of Lo et al. (2012), who found statistically-significant increases in prevalence odds of WOMAC pain in the presence of thrust during weight-bearing activities only. It is possible that our larger sample size afforded us greater power to detect statistically-significant associations. Another possible explanation is that the effects of thrust on consistent pain across all WOMAC activities may only be observable in a longitudinal study of worsening, and not a cross-sectional study of prevalence (i.e., after a two-year period, thrust causes sufficient damage to the knee to elicit pain during both weight-bearing and non-weight-bearing activities).

Previous work has shown an association between varus thrust and incident and worsening medial bone marrow lesions (Wink et al., 2017). Bone marrow lesions are strongly associated with the presence of pain in knee osteoarthritis (Felson et al., 2001; 2007). We therefore consider that the association of varus thrust to incident and worsening knee pain is due at least in part to the development or enlargement of bone marrow lesions.

Knee pain intensity is a predictor of total knee joint replacement in osteoarthritis (Conaghan et al., 2010). Mitigating knee pain through inexpensive and non-invasive therapies that modify knee thrust and its associated joint loads is therefore of interest, especially for those wishing to delay total knee replacement. These therapies include gait retraining, exercise regimes, and bracing. In a case study of a single subject with varus

knee thrust, Hunt et al. (2011) showed that modifying gait through increased toe-out and trunk lean decreased the magnitude of the varus thrust angle as well as the peak knee adduction moment (KAM). Bennell et al. (2015) found that a neuromuscular exercise regime focusing on trunk and lower extremity position and movement quality improved pain and physical function in those with thrust, though thrust during the course of the exercise intervention was not assessed. Pollo et al. (2002) observed a trend toward reduction in external knee varus moments associated with varus thrust as a result of valgus knee bracing. Testing these clinical interventions requires quantitative measures of thrust and associated joint loads (Hunt et al., 2011); these measures were not available in our study. Furthermore, more research into the anatomic and/or sensorimotor causes of knee thrust is required in order to create potential interventions for thrust.

This study has several limitations related to the assessment of the exposure (varus thrust) and the primary outcome (pain). In our study, thrust was assessed visually from high-speed videos in a clinical setting. This method allows the observer to visualize the varus position of the knee, but quantitative measures associated with thrust, such as varus angle and angular velocity (Chang et al., 2013; Sosdian et al., 2016), cannot be accurately estimated; however, our method for assessing thrust (and subsequent pain risk) is likely similar to what might be employed in a clinic setting where quantitative methods are unavailable. A second limitation is that thrust was only assessed by one observer. While we report good intra-rater reliability, our findings would be strengthened with measures of inter-rater reliability. Iijima et al. (2015) reported good inter-rater reliability ( $\kappa = 0.73$ ) for visual assessment of thrust, using a similar protocol to ours. Assessing pain

longitudinally also brings limitations. Our definition of worsening pain is a net increase in WOMAC score over two years; however, as pain levels can increase and decrease over time, this definition leaves us unaware of more nuanced changes in participants' pain levels within the study period. The questions on the WOMAC instrument refer to participants' pain experience over a period of 30 days; thus, we remain confident that participants' pain responses refer to consistent levels of pain at baseline and two years.

In summary, our results indicate that varus thrust is a risk factor for incident and worsening WOMAC knee pain, regardless of baseline OA status. Targeting varus thrust through non-invasive therapies could reduce the risk of knee pain in older adults with or at risk for knee OA.

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## **CHAPTER 4.**

### **THE BIOMECHANICAL AND CLINICAL EFFECTS OF THRUST ON NEIGHBORING JOINTS**

#### **Part 1: Quantifying Joint Angles and Moments in a Biomechanical Model of Unilateral Varus Knee Thrust**

#### **Part 2: Association of Varus Knee Thrust with Incident Frequent Pain at the Low Back, Hip, Ankle, and Foot**

## CHAPTER 4, PART 1

### QUANTIFYING JOINT ANGLES AND MOMENTS IN A BIOMECHANICAL MODEL OF UNILATERAL VARUS KNEE THRUST ABSTRACT

*Objective.* To evaluate frontal plane joint angles and moments in the knee as well as the hip and ankle in the affected and unaffected limb of a single subject with unilateral varus knee thrust using a biomechanical model.

*Method.* A three-dimensional kinetics and kinematics data set of a 61-year old male subject with unilateral knee osteoarthritis (OA) was analyzed. Variables of interest included joint angles and moments for the knee, hip, and ankle.

*Results.* Varus thrust was observed in the left knee, which averaged a maximum varus angle of  $9.25^{\circ}$ . Conversely, at approximately 20% into the stance phase, the frontal plane angle for the right (comparator) knee averaged  $0.84^{\circ}$  valgus. The left hip was in an abducted position throughout stance, and the left ankle was in an everted position from 10-90% of stance and moved into an inverted position in the last 10% of stance. The right hip remained in an adducted position throughout stance and moved toward a neutral position in late stance, and the right ankle was largely in an inverted position throughout stance. The external knee adduction moment in the left knee was consistently high throughout stance, with an average maximum of 0.439 Nm/kg over four trials occurring at between 62% and 73.2% of stance. Compared to the right limb, the left external hip adduction moment was much lower during stance for the left, with an average maximum of 0.498 Nm/kg over four trials occurring at between 62% and 73.2% of stance. The right

ankle had an external eversion moment from heel strike until approximately 70% stance, after which it had an external inversion moment. In the left ankle, a large external eversion moment persisted through the first 90% of stance with a small peak external inversion moment occurring at approximately 95% of stance.

*Conclusions.* While this study is limited, our findings support the existence of differences in magnitude or trajectory of frontal plane hip, knee, and ankle angles and moments between limbs with and without thrust. These findings justify investigation into the clinical implications of thrust proximal and distal to the knee.

## **INTRODUCTION**

Dynamic gait alterations in patients with knee osteoarthritis (OA) have been well documented (e.g., Astephen et al., 2008; Duffell et al., 2017; Foroughi et al., 2010; Hall et al., 2017; Heiden et al., 2009; Kaufman et al., 2001; Mills et al., 2013). These alterations include changes in frontal, sagittal, and horizontal plane angles and moments, among other variables. Frontal plane mechanics during gait are especially of interest, as these are thought to be responsible for asymmetric medial-lateral joint loads that contribute to a high prevalence of medial tibiofemoral OA. Varus knee thrust, an abrupt change in the frontal-plane angle of the knee during the weight-acceptance phase of gait, is commonly observed in OA patients and is a documented risk factor for OA-related structural damage to the medial compartment of the knee joint (Chang et al., 2004; Wink et al., 2017) as well as knee pain (Lo et al., 2012). Due to the public-health significance of OA and associated risk factors, there have been numerous clinical epidemiological

studies of thrust; however, as thrust is a biomechanical event, the kinetic and kinematic consequences of thrust are also of importance.

Thrust can be observed visually and therefore has great utility in a clinical setting; however, quantitative assessment of thrust through gait analysis provides great insight into the kinetics and kinematics of this phenomenon. Biomechanical studies on varus thrust have primarily focused on effects at the knee joint. Chang et al. (2004) found that knees with varus thrust had a significantly greater knee adduction moment (KAM) compared to knees without a thrust. Kuroyanagi et al. (2012) showed a statistically-significant correlation between the magnitude of varus thrust (in degrees) and the KAM. Chang et al. (2013) demonstrated that knees with a varus thrust also had a significantly greater peak knee varus angle during the entire stance phase and a greater peak knee varus angular velocity compared to knees without varus thrust, even after adjusting for static knee alignment status. Mahmoudian et al. (2016) found that the magnitude of varus thrust was significantly correlated with both the first and second peak KAM.

In focusing solely at the knee, these studies failed to acknowledge that biomechanical events at the knee do not occur in isolation; rather, they play a role along the kinematic chain of the lower extremity, and are likely to affect the mechanics of neighboring joints. Our objective was to evaluate frontal plane joint angles and moments in the knee as well as the hip and ankle in the affected and unaffected limbs of a single subject with unilateral varus knee thrust using a biomechanical model. This hypothesis-generating pilot examination will provide rationale for further study of joint loading proximal and distal to the knee in larger samples of varus thrust patients.

## **METHODS**

### *Data Set*

A three-dimensional kinematics and kinetics data set of a patient with medial knee OA with varus thrust was obtained from the Hospital for Special Surgery (New York, NY). The subject was a 61-year-old male, 1.7 meters (66.9 inches) in height and 78.4 kg (172.8 lb) in weight (BMI = 27.1). The left (thrust) limb had medial knee OA (KL = 3), and the right (unaffected) limb was asymptomatic. There was no length discrepancy between the right and left limbs.

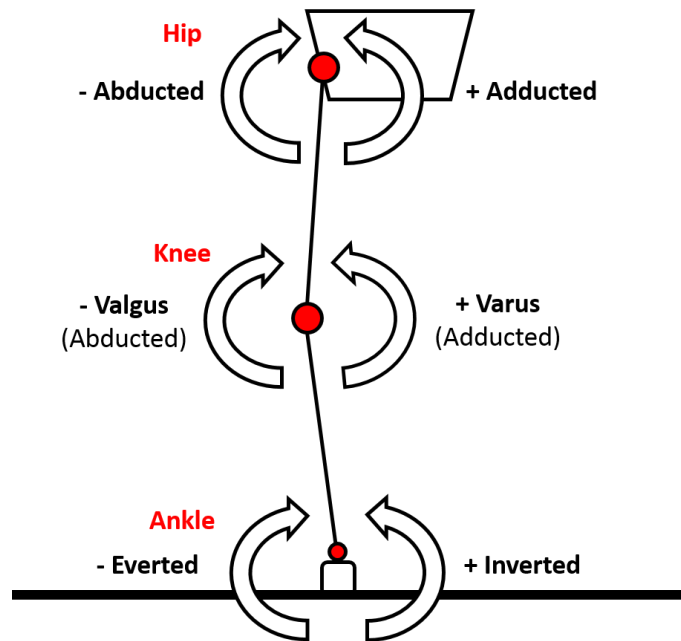
### *Data Analysis*

Force plate data and angles and moments for the pelvis, thigh, shank, foot, hip, knee, and ankle during the stance phase for each leg were obtained using Visual3D (C-Motion, Inc., Germantown, MD). To ensure optimal accuracy for the analyses, these data were exported for multiple trials for each leg.

### *Definitions of Variables of Interest*

The variables of interest in this study are frontal plane angles and moments for the knee, hip, and ankle during the stance phase of gait. The knee angle is defined as the angle of the shank relative to the thigh and presented such that a positive angle represents a varus knee and a negative angle represents a valgus knee. The hip angle is defined as the angle of the thigh relative to the pelvis and presented such that a positive angle represents an adducted hip and a negative angle represents an abducted hip. The ankle angle is defined as the angle of the foot to the shank and presented such that a positive

angle represents an inverted ankle and a negative angle represents an everted ankle (Figure 4.1).



**Figure 4.1.** Illustration of sign conventions for hip, knee, and ankle angles. Right limb, anterior view.

A joint moment is a rotational force acting on a segment and is measured as the magnitude of the force multiplied by the length of the force moment arm (i.e., the perpendicular distance of the force from its axis of rotation). Internal moments are the products of internal forces (i.e., muscle forces) and the internal moment arms; whereas external moments are the products of external forces (i.e., gravity) and the external moment arm (i.e., distance between the axis of rotation and the perpendicular intersection with the external force). External moments (equal to and opposite of the internal moments) are presented here. Results will first be presented for the right (non-thrust, comparator) limb and then for the left (thrust) limb.

## RESULTS

### **Right (non-thrust, comparator) limb.**

#### *Frontal Plane Joint Angles*

The average net varus excursion for the right knee, defined as the difference between the peak varus angle and the knee angle at heel strike, was 3.69° and occurred at approximately 36% of the stance phase. During the early loading phase (approximately 20% of stance), the frontal plane angle for the right knee averaged 0.84° valgus over three trials (**Figure 4.2**, solid blue line). The right hip was in an adducted position throughout stance and moved toward a neutral position in late stance (**Figure 4.3**, solid blue line). At 20% of stance, the angle of the right foot relative to the right shank (i.e., the right ankle angle) was at an average of approximately 0.60° of eversion across three trials and moved into an inverted position in late stance (**Figure 4.4**, solid blue line).

#### *Frontal Plane Joint Moments*

The right knee followed a typical external knee adduction moment pattern, with a first peak (averaging 0.416 Nm/kg over three trials) in early stance and a second, smaller peak (averaging 0.287 Nm/kg over three trials) in late stance (**Figure 4.5**, solid blue line). The right hip exhibited a two-peaked external hip adduction moment throughout stance phase. The first peak averaged 0.853 Nm/kg over three trials and the second peak averaged 0.689 Nm/kg over three trials (**Figure 4.6**, solid blue line). We observed an external eversion moment around the right ankle from heel strike until approximately 70% stance, after which we observed an external inversion moment with an average peak

of 0.156 Nm/kg over three trials (**Figure 4.7**, solid blue line). This trajectory is similar to that reported in normative studies (Hunt and Smith, 2004; Resende et al., 2015).

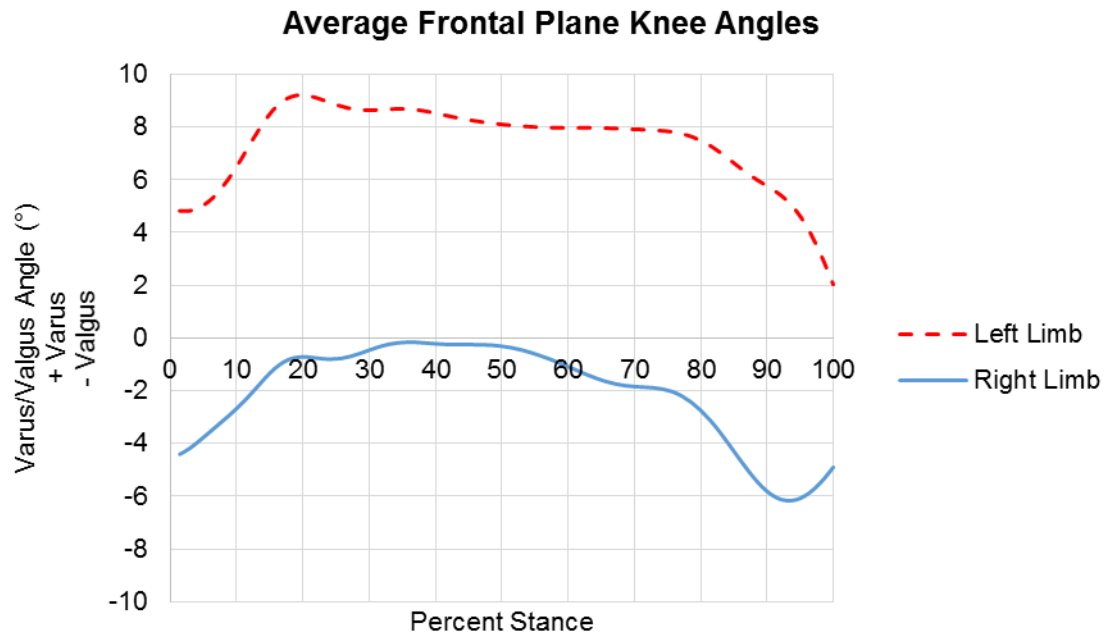
### **Left (thrust) limb.**

#### *Frontal Plane Joint Angles*

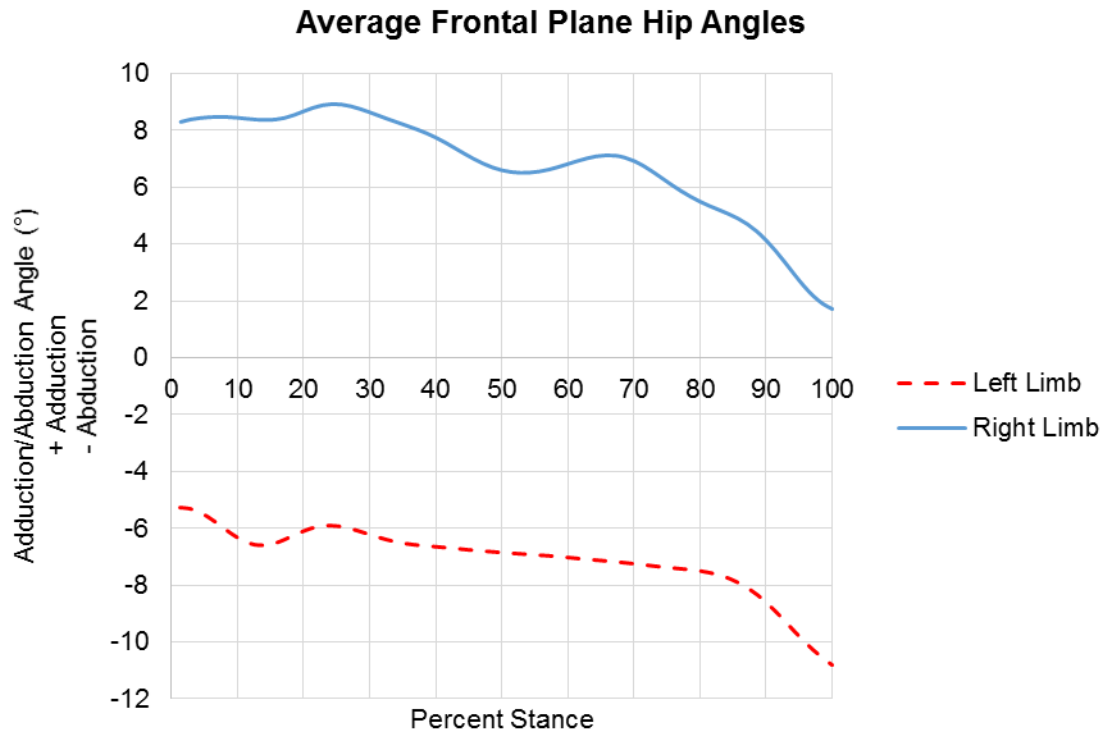
The left knee averaged a maximum varus angle of 9.25° over four walking trials. The average net varus excursion, defined as the difference between the peak varus angle and the knee angle at heel strike, was 4.42°. This peak varus angle occurred approximately 20% into the stance phase (**Figure 4.2**, red dashed line). The hip was in an abducted position throughout stance and had an average peak of approximately 6.59° of abduction between 10-20% of stance (**Figure 4.3**, red dashed line). The left ankle peaked at an average of 4.15° of eversion over four trials at approximately 20% of stance (corresponding with the timing of the left peak frontal plane knee angle), and moved into an inverted position in the last 10% of stance (**Figure 4.4**, red dashed line).

#### *Frontal Plane Joint Moments*

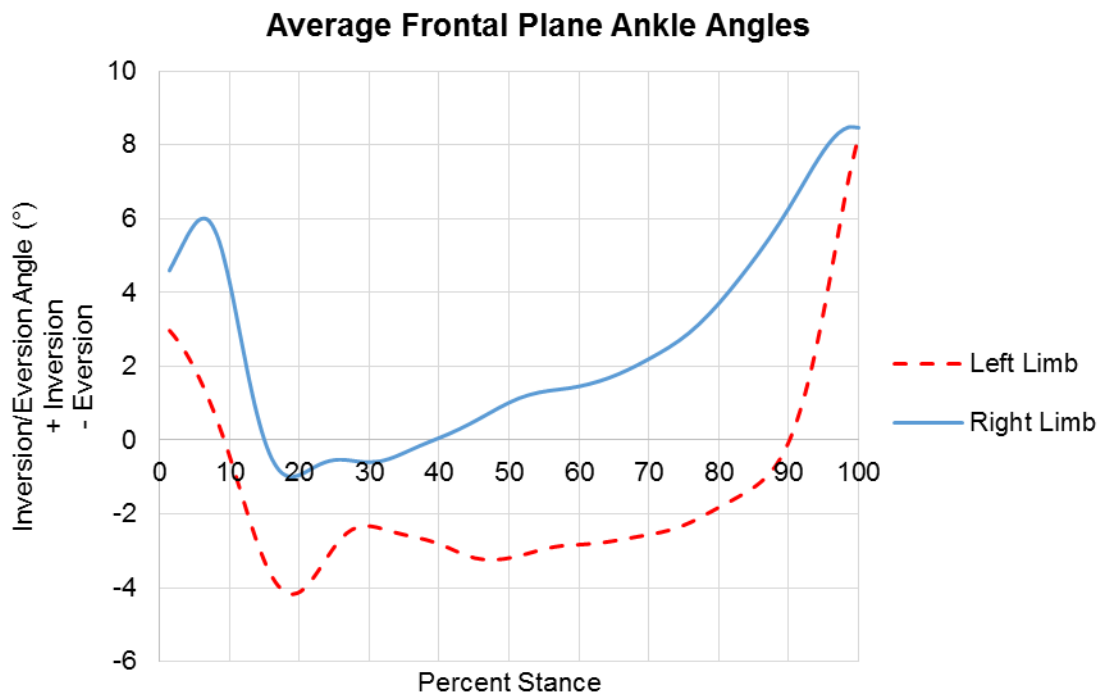
The external knee adduction moment in the left knee was consistently high throughout stance, with an average maximum of 0.439 Nm/kg over four trials occurring at between 62% and 73.2% of stance (**Figure 4.5**, red dashed line). The left external hip adduction moment was much lower during stance compared to the contralateral limb, with an average maximum of 0.498 Nm/kg over four trials occurring at between 62% and 73.2% of stance (**Figure 4.6**, red dashed line). In the left ankle, a large external eversion moment persisted through the first 90% of stance with a small peak external inversion moment occurring at approximately 95% of stance (**Figure 4.7**, red dashed line).



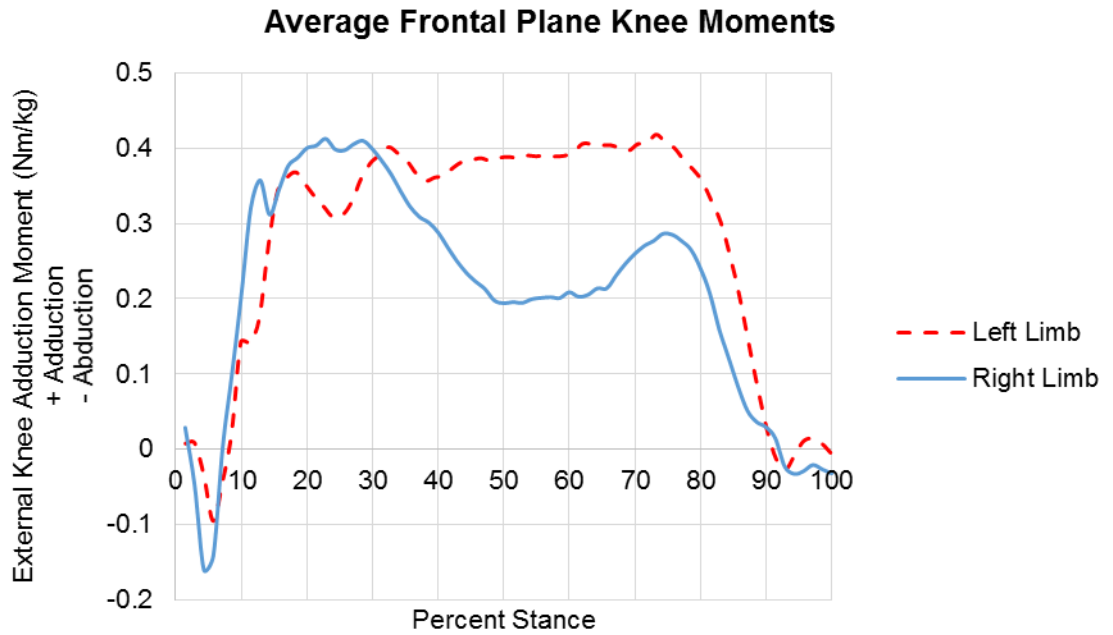
**Figure 4.2.** Average frontal plane knee angles throughout stance phase for the left (thrust) limb (red dashed line) and the right (unaffected) limb (solid blue line). Positive values indicate a varus position; negative values indicate a valgus position.



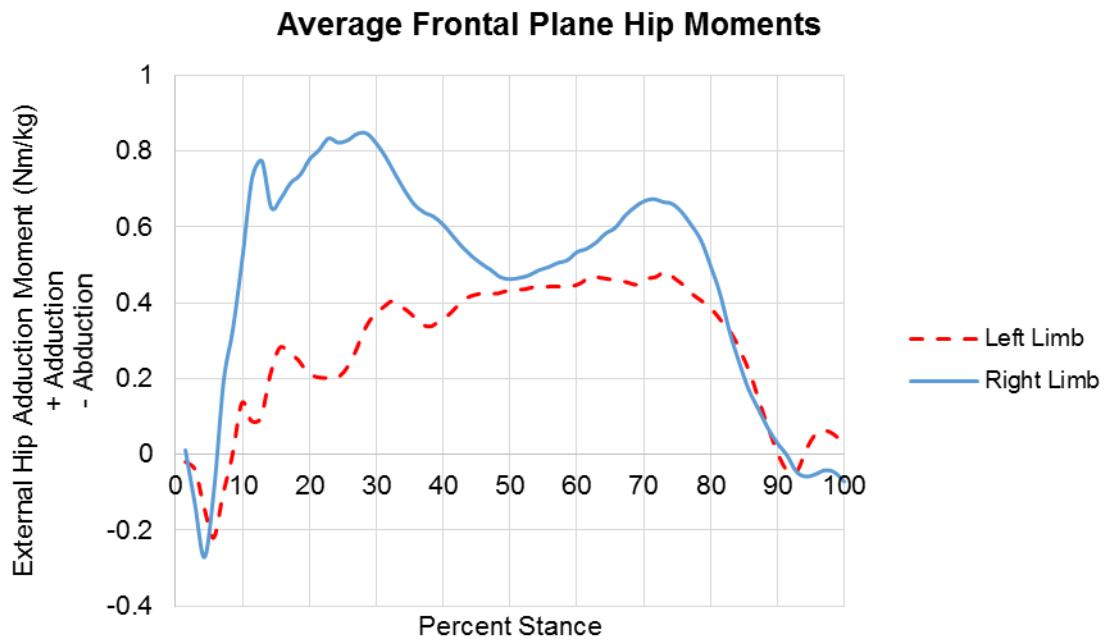
**Figure 4.3.** Average frontal plane hip angles throughout stance for the left (thrust) limb (red dashed line) and the right (unaffected) limb (solid blue line). Positive values indicate an adducted position; negative values indicate an abducted position.



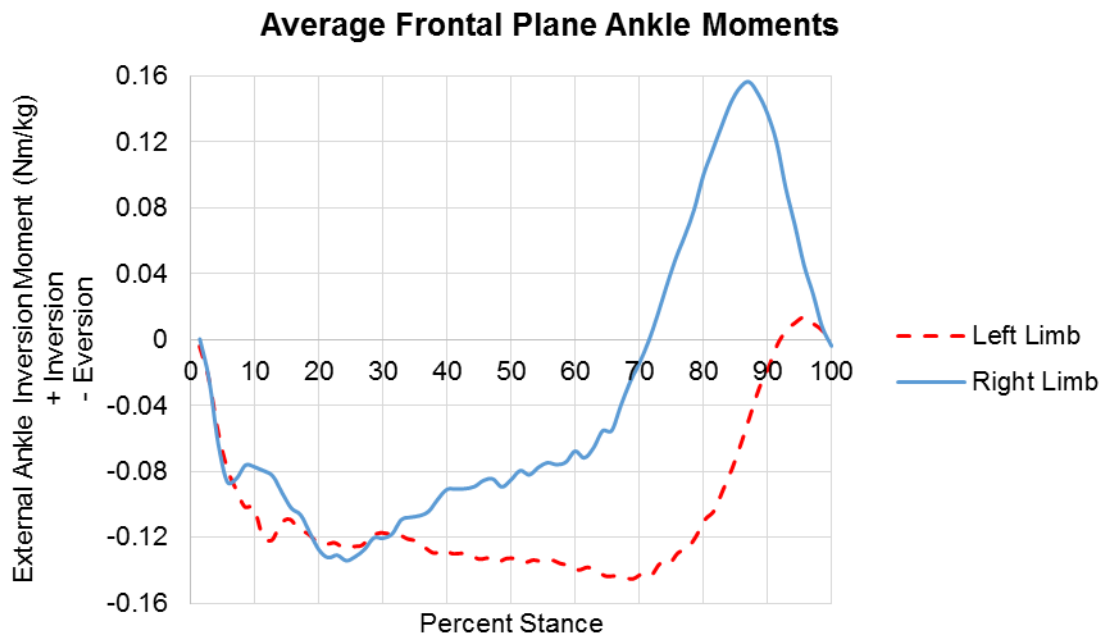
**Figure 4.4.** Average frontal plane ankle angles throughout stance for the left (thrust) limb (red dashed line) and the right (unaffected) limb (solid blue line). Positive values indicate an inverted position; negative values indicate an everted position.



**Figure 4.5.** Average external frontal plane knee moments throughout stance phase for the left (thrust - red dashed line) and right (unaffected - blue solid line) limbs. Positive values indicate an external adduction moment and negative values indicate an external abduction moment.



**Figure 4.6.** Average external frontal plane hip moments throughout stance phase for the left (thrust - red dashed line) and right (unaffected - blue solid line) limbs. Positive values indicate an external adduction moment and negative values indicate an external abduction moment.



**Figure 4.7.** Average external frontal plane ankle moments throughout stance phase for the left (thrust - red dashed line) and right (unaffected - blue solid line) limbs. Positive values indicate an external inversion moment and negative values indicate an external eversion moment.

## DISCUSSION

Previous studies on varus thrust have provided varying definitions of thrust based in quantitative biomechanical analysis as well as visual observation; whether the subject in this study would be classified as having a thrust based on both quantitative and visual observation is unclear. Sossian et al. (2016) defined thrust as the largest and most abrupt frontal plane movement during the first 30% of stance; in order to be defined as thrust, the largest frontal plane movement also had to coincide with the peak knee angular velocity. Chang et al. (2013) noted a similar co-occurrence of peak varus-valgus angle and peak varus-valgus angular velocity in knees with varus thrust. In our study, the peak varus angle in the affected knee occurred within the first 20% of stance, consistent with

these biomechanical definitions of thrust. While the right (asymptomatic) knee maintained a valgus position throughout stance, we note that it did follow a similar trajectory toward a less-valgus position, though the peak varus angle did not occur until approximately 36% of stance. Overall, the net varus excursion was greater for the affected limb than for the asymptomatic limb, consistent with the findings of others (Hunt et al., 2011; Mahmoudian et al., 2016). The trajectories (not shown) of the knee varus-valgus angular velocity between the left and right limbs were similar throughout the stance phase, with the peak velocity occurring between 10-20% of stance for both knees.

The peak external KAM values between the comparator and thrust limbs were similar (0.416 Nm/kg and 0.439 Nm/kg, respectively), and the magnitude of the external KAM in early stance was similar between the two limbs. We observed a consistently-high external KAM throughout the stance phase of gait in the thrust limb compared to the comparator limb, however, such that the magnitude of the thrust limb external KAM was much higher than that of the comparator limb in late stance. These results differ slightly from those of Mahmoudian et al. (2016) who, in a study of women with medial knee OA, found a statistically-significantly higher first *and* second peak external KAM in varus thrust knees compared to knees without varus thrust. Others have suggested that the knee adduction angular impulse, rather than peak KAM, is a more comprehensive measure of cumulative medial knee loads (e.g., Chang et al., 2015; Creaby et al., 2010). The angular impulse, calculated as the time integral of the moment curve (i.e., the area under the curve) represents both magnitude and duration of the load. While not calculated in our

study, a comparison of the KAM curves for the thrust and comparator limbs indicates a higher knee adduction angular impulse in the thrust limb.

The hip angles observed here (i.e., the angle of the thigh relative to the pelvis) for both limbs differ somewhat from what would be expected based on normative values (e.g., Kadaba, 1990; Simoneau, 2002). Altered trunk (e.g., ipsilateral trunk lean) or pelvic (e.g., pelvic drop) kinematics, as well as the static alignment of the lower limb, may have affected these trajectories. The external hip adduction moment around the thrust limb is overall lower than the asymptomatic limb, indicative of a smaller internal torque from the hip abductor muscles (i.e., the tensor fascia lata, gluteus medius, and gluteus minimus). The reduced torque of hip abductors could also be related to altered trunk and pelvic kinematics; alternately, they could be related to reduced hip muscle strength (Chang et al., 2005). Rutherford and Hubble-Kozey (2009) reported that peak activation of the gluteus medius in early stance did not explain variation in the external hip adduction moment, but acknowledged that other muscles (such as tensor fascia lata) and passive support structures not evaluated in their study may also be contributing factors to this moment.

Our external hip adduction moment trajectories between the affected and unaffected limbs are similar to those reported in previous studies of healthy and knee OA subjects (Astefhen et al., 2008; Chang et al., 2005; Mündermann et al., 2005; Rutherford and Hubble-Kozey, 2009). Chang et al. (2005) showed that among knees with OA, non-progressing knees had greater peak internal hip abduction (or external hip adduction) moments compared to progressing knees, and that a greater internal hip abduction

moment was protective against OA progression over 18 months. It is therefore not surprising that we observed a higher external hip adduction moment in the asymptomatic limb.

In the left (thrust) limb, we observed that the foot everts in the first 10% of stance and remains in an everted position relative to the shank between 10 and 90% of stance. This is not surprising, given the varus position of the shank. At approximately 20% of stance (concurrent with the peak varus angle in the left knee), there is a small reversal in position in which the ankle abruptly inverts until approximately 30% of stance. We also observed a large external ankle eversion moment that persisted through the first 90% of stance, followed by a small external inversion moment in the last 10% of stance. These external moments correspond to internal moments of equal magnitude in the opposite direction.

Electromyographic (EMG) data show that activation of tibialis posterior, a primary inverter of the ankle, peaks once in early stance and again in midstance (Maharaj et al., 2016). The tibialis posterior (as well as the tibialis anterior<sup>3</sup>) may be responsible for the internal inversion moments observed in the first 70% of stance for the asymptomatic limb and the first 90% of stance for the thrust limb. EMG studies have also demonstrated maximum activation of the fibularis longus muscle, the primary everter of the ankle, at approximately 75% of stance in normal gait (Hunt and Smith, 2004). It is likely that eccentric contraction of the fibularis longus is responsible for the internal eversion

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<sup>3</sup> The tibialis anterior, in addition to being an ankle inverter, is also a primary dorsiflexor of the ankle. EMG studies of the tibialis anterior would show activation during both frontal plane (inversion) and sagittal plane (dorsiflexion) motion during stance.

moment that counters the external inversion moment, stabilizing the ankle as it inverts in late stance. This moment is much smaller in magnitude and occurs much later in stance in the thrust limb compared to the asymptomatic limb. Given the difference in frontal plane moment trajectories between the two limbs, it is feasible that there are also differences in the interaction between ankle inverters and everters that control frontal plane stability of the ankle joint.

Our frontal-plane ankle moment findings are similar to those of Mündermann et al. (2005), who found a reduction in maximum external inversion moment in terminal stance in OA patients compared to controls. In a study of young, healthy subjects, Resende et al. (2015) reported significant ( $p < 0.001$ ) differences in the trajectories of frontal plane ankle moments and rearfoot angles between control limbs and limbs wearing a lateral-wedge insole: the limb wearing the insole had a greater external ankle eversion moment between 15 and 90% of stance and a greater rearfoot eversion angle throughout stance. These differences in trajectories were similar to what we observed between the asymptomatic and thrust limb.

It is important to note that this is an observational study of biomechanical differences between a limb with varus thrust and an asymptomatic limb, and not an analysis of biomechanical effects of thrust. Within the context of this study, it is not possible to determine whether differences in joint angles and moments occur as a result of thrust or as concurrent gait alterations. This study and others (e.g., Chang et al., 2013; Kuroyanagi et al., 2012) show that the peak varus excursion associated with varus thrust occurs in the first 20-33% of stance, however; thus it is feasible that deleterious

biomechanical consequences of thrust may occur along the lower limb in mid-to-late stance.

This study has several additional limitations. The biomechanical analysis of a single subject with unilateral varus thrust, while not unprecedented (Hunt et al., 2011), is not ideal. This study is not generalizable to all persons with thrust and cannot be used to make conclusions on the effects of thrust beyond the knee. With a single subject it is also not appropriate to test for statistically-significant differences in joint angles, angular velocities, and moments between the affected and unaffected limbs. Other factors such as body mass and gait speed are known to be related to variability in joint moments (Rutherford and Hubley-Kozey, 2009; Telfer et al., 2017); multiple subjects would allow for better accounting for these variables. It is important to note that in addition to exhibiting unilateral varus thrust, the study subject also had asymmetric knee OA (i.e., one limb symptomatic, one asymptomatic). Wide variability exists in the gait patterns of knee OA versus control patients due to differences in age, knee alignment, disease severity, and walking speed (Baert et al., 2013; Heiden et al., 2009). Creaby et al. (2012) found that between-limb asymmetries in gait occur in individuals with unilateral structural disease; thus the symptomatic OA status of the left limb may have affected the biomechanics of the lower extremity independently of the thrust<sup>4</sup>. Alternately, OA may

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<sup>4</sup> This is particularly relevant in the case of the external KAM pattern observed in the thrust limb, namely the similar magnitude of the first peak KAM between the thrust and comparator limbs and the elevated “second peak” in the thrust limb compared to the contralateral limb. While Mahmoudian et al. (2016) showed both an elevated first and second peak in patients with thrust compared to patients without thrust, they also observed a significantly-elevated second-peak external KAM with no significant difference in first-peak external KAM in established OA patients compared to early OA patients and healthy controls without taking thrust status into

be a mediator in the relationship of thrust to biomechanical gait changes (Aststephen et al., 2008). While we treat the right limb as a comparative control and assume that it represents a normal gait pattern, the extent to which the affected limb affects the gait pattern of the contralateral (unaffected) limb is also unknown. In order to be validated, this study would need to be repeated in a larger sample, preferably in subjects with symmetric knee OA status.

While limited in scope, this is the first investigation into altered biomechanics proximal and distal to the knee in a subject with varus knee thrust. We observed differences in the trajectories of the position and moment of the knee, hip, and ankle during stance between an osteoarthritic limb with varus thrust and an asymptomatic limb with a smaller varus excursion in gait. While not observed in this study, we can hypothesize that there are differences in muscle activation and joint forces between the affected and unaffected limbs as well. Future studies on larger samples to broaden and generalize these findings are warranted. Importantly, these preliminary findings provide the rationale for clinical investigation of painful injury proximal and distal to the knee in the context of varus thrust.

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account. Therefore, the pattern we observed may be related to the established OA status (KL = 3) of our subject's left limb, rather than the thrust status.

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## CHAPTER 4, PART 2

### ASSOCIATION OF VARUS KNEE THRUST WITH INCIDENT FREQUENT PAIN AT THE LOW BACK, HIP, ANKLE, AND FOOT

#### ABSTRACT

*Objective.* To determine the effects of varus knee thrust observed during walking on the two-year incidence of self-reported frequent pain at the low back, hip, ankle, and foot.

*Method.* Participants in the Multicenter Osteoarthritis (MOST) Study were evaluated. Varus thrust was observed visually from high-speed videos of self-paced forward walking trials. Frequent low back, hip, ankle, and foot pain at baseline and two years was self-reported using a homunculus. Logistic regression with generalized estimating equations or paired analyses was used to estimate the odds of incident frequent pain at individual and combined sites in the presence of varus thrust, adjusting for age, sex, race, BMI, and gait speed.

*Results.* 1649 participants contributed 3278 knees. Individual site analyses demonstrated that limbs with knee thrust had 1.34 (95% CI: 1.03, 1.73) times the odds of incident frequent hip pain and 1.60 (95% CI: 1.18, 2.17) times the odds of incident frequent foot pain compared to limbs without thrust. Limbs with thrust also had significantly increased odds of proximal (low back or hip) and distal (ankle or foot) pain and total lower limb pain overall compared to limbs without thrust.

*Conclusion.* Varus thrust observed during walking is associated with two-year incidence of frequent joint pain both proximal and distal to the knee. Interventions that

target varus knee thrust may also be effective in preventing painful injury at neighboring joints.

## **INTRODUCTION**

Musculoskeletal pain is an impactful problem among older adults, having effects on general health, mental health, disability, and lost productivity in the workforce (Keenan et al., 2006). In a sample of over 16,000 older adults, 39.11% reported joint pain, swelling, or stiffness lasting  $\geq 6$  weeks over a period of 3 months (Keenan et al., 2006). Low back and lower limb pain is especially of interest in this population, due to an associated risk of functional impairment. Back pain is highly prevalent in patients with knee OA (Stupar et al., 2010; Suri et al., 2010; Wang et al., 2016; Wolfe et al., 1996), and up to one-fifth of older adults report frequent hip pain (Dawson et al., 2004). Ankle and foot conditions are also widespread in older adults: the estimated population prevalence of ankle joint pain in older adults is 14.9% (Dunn et al., 2004); though prevalence of ankle OA is only estimated at 1-4% (Kraus et al., 2013; Valderrabano et al., 2009). Foot pain, when defined as tenderness to palpation, has an estimated total prevalence of 30.9%, with varying prevalence by region (Dunn et al., 2004).

Multiple joint problems are particularly impactful in older adult populations. For instance, low back pain is significantly associated with WOMAC knee pain (i.e., pain during functional activity) as well as frequent pain at the hip, ankle, and foot (Suri et al., 2010). Hip pain is also frequently observed in combination with back, knee, and foot pain (Keenan et al., 2006). In addition to the frequency of pain at multiple joints along a single limb, there is evidence that the evolution of lower limb OA leading to joint replacement

also follows a non-random biomechanically-based pattern (Shakoor et al., 2002). These facts taken together strongly indicate that biomechanical alterations of the lower limb during gait should be a target of investigation for lower limb pain.

Varus knee thrust is an observable abrupt change in the frontal plane angle of the knee during the weight-acceptance phase of gait, with a return to a neutral or less-varus position during late stance and toe-off. Varus thrust has been previously linked to increased progression of radiographic knee OA (Chang et al., 2004), incident and worsening medial tibiofemoral bone marrow lesions (Wink et al., 2017), and prevalent knee pain, stiffness, and physical functioning problems (Fukutani et al., 2016; Iijima et al., 2015; Lo et al., 2012).

The relation of thrust to knee biomechanics, particularly the external knee adduction moment and knee angular velocity, has been well-documented (e.g., Chang et al., 2004, 2013). The body of research on varus knee thrust has yet to examine the effects of thrust on the entire kinematic chain of the lower extremity, in other words, the relation of thrust to the risk of painful injury to neighboring joints such as the ankle and hip, as well as more removed sites such as the foot and low back. It has been suggested that guidelines for the management of joint problems should be focused on multiple joints, rather than a single joint only (Keenan et al., 2006; Suri et al., 2010). Previous studies have examined lower limb gait changes secondary to the knee in knee OA patients (Aststephen et al., 2008; Mündermann et al., 2005) and suggested that these gait changes may be compensatory in nature.

The objective of this study is to determine the relation of varus knee thrust observed during walking to the two-year incidence of self-reported frequent joint pain proximal and distal to the knee, specifically at the low back, hip, ankle, and foot. We hypothesized that limbs with thrust have higher odds of incident pain in ipsilateral neighboring joints compared to limbs without thrust.

## **METHODS**

### *Sample*

The Multicenter Osteoarthritis Study (MOST) is a prospective, observational cohort study of knee OA in older Americans that have OA or are at an increased risk of developing it. Factors considered to contribute to an increased risk of knee OA included being overweight; having knee symptoms without radiographic OA; and having a prior knee injury or previous knee surgery. Subjects were recruited from two communities: Birmingham, Alabama, and Iowa City, Iowa. The MOST protocol was approved by the Institutional Review Boards at the University of Iowa; University of Alabama, Birmingham; University of California, San Francisco; and Boston University. Details of the MOST sample, including exclusion criteria, are described elsewhere (Segal et al., 2013).

Gait data were collected from 2,768 participants at the MOST 60-month clinic visit. Participants were instructed to walk across a 4.9-meter pressure-sensitive gait carpet, during repeated trials at a self-selected normal and a more hurried pace. A high-speed (60 Hz) video camera positioned at one end of the walkway recorded each subject's gait pattern. GAITRite resident software (GAITRite Inc., Clifton, NJ,

<http://www.gaitrite.com>) was used to compute spatiotemporal gait parameters such as walking velocity.

MOST participants in the 60-month gait exam had to be able to walk independently over short indoor distances without the use of a walking aid or orthotic knee brace. Participants with recent (< 6 weeks) lower limb injury resulting in restricted weight bearing for over one week, recent hospitalization for a cardiovascular or respiratory disorder, lower limb amputation proximal to the toes, or difficulty walking because of a neurological condition were excluded.

#### *Assessment of Varus Knee Thrust*

A single trained observer (AW), blinded to knee disease status, assessed thrust from high-speed videos of participants in the MOST 60-month gait exam during two self-paced walking trials. Participants dressed in short pants and their customary shoes. Skin markers were placed over the centers of the patellae and tibial tuberosities to facilitate visualization of the knee. Knees were excluded from the thrust assessment if a clear view of either marker was obscured by clothing. Thrust was defined as the dynamic worsening or abrupt onset of varus alignment during the weight acceptance phase of gait, with a return to more neutral alignment during the lift-off and swing phases (Chang et al., 2010). Thrust was initially graded on a Likert-type scale as “definitely present,” “probably present,” “probably absent,” and “definitely absent.” Further, knees with thrust “definitely present” or “probably present” were further characterized as exhibiting thrust during “all steps,” “greater than half (but not all) of steps,” and “fewer than half of steps.” For the purposes of the current study, a simplified dichotomous variable was

defined, wherein thrust was considered present when thrust was “definitely present” during any steps or “probably present” during “all steps.” Intra-rater reliability for varus thrust was substantial ( $\kappa = 0.73$ ).

#### *Assessment of frequent lower limb joint pain*

Frequent pain at the low back, hip, ankle, and foot was self-reported at baseline (60 months) and two years (84 months) using joint pain homunculus diagrams. A bubble was placed over regions and joints of the whole body and foot, and participants were asked to “fill in the bubbles...to show which joints have had pain, aching, or stiffness on most days in the past 30 days.” Foot pain was defined as any affirmative pain response on the dorsal or plantar surface of the foot. For back pain, a back homunculus was divided into regions, and participants were instructed to mark all areas on the back where pain in the past 30 days was usually located. Low back pain was defined as pain in the lower back or buttocks. Among subjects reporting no pain at 60 months, incident pain is defined as pain at any site at 84 months.

#### *Data Analysis*

Logistic regression was used to evaluate the odds of incident frequent pain at each individual site according to presence of varus thrust, adjusting for age, sex, race, BMI, and gait speed and, for the limb-based analyses, using GEE or paired analyses to account for correlation between two limbs from the same subject. In order to evaluate the relation of thrust to incident pain within a broader region of the lower limb while increasing our power to detect any true associations, these analyses were repeated, first combining sites proximal (i.e., hip or low back) and distal (i.e., ankle or foot) to the knee, and then

combining all lower limb sites. Results are reported as adjusted odds ratios with associated 95% confidence intervals. Statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

## RESULTS

Our study sample consisted of 1649 persons contributing 3278 knees. Sample demographics are listed in **Table 4.1**. Varus thrust was observed in 31.5% of knees.

**Table 4.1.** Study sample demographics.

<b>Person Based Demographics (n = 1649)</b>	
<b>Age</b> (Mean $\pm$ S.D., years)	67.7 $\pm$ 7.6
<b>BMI</b> (Mean $\pm$ S.D., kg/m <sup>2</sup> )	30.1 $\pm$ 5.9
<b>Sex</b> (% Female)	60.3
<b>Race</b>	
- % White	88.4
- % Black	10.3
- % Other	1.3
<b>Site</b> (% Alabama)	41.5
<b>Knee Based Demographics (n = 3278)</b>	
<b>Varus Thrust Presence</b> (%)	31.5
<b>Baseline Radiographic TF OA</b> (% KL $\geq$ 2)	41.8
- % KL = 2	17.6
- % KL = 3	19.6
- % KL = 4	4.7

When pain locations were examined individually, we found that knees with varus thrust had 1.34 times the odds (95% CI: 1.03, 1.73) of incident ipsilateral hip pain and 1.60 times the odds (95%: CI 1.18, 2.17) of incident ipsilateral foot pain compared to knees without thrust. Nonsignificant results ( $p = 0.08$ ) suggested that persons with varus thrust in at least one knee may have increased odds of incident low back pain compared to persons without thrust. No statistically-significant association was found between varus thrust and incident ankle pain ( $p = 0.19$ ).

Combining proximal and distal outcomes yielded statistically significant results. After adjusting for covariates, knees with thrust had 1.26 times (95% CI: 1.01, 1.58) the odds of incident proximal (hip *or* low back) pain and 1.34 times (95% CI: 1.05, 1.68) the odds of incident distal (ankle *or* foot) pain compared to knees without thrust. Knees with thrust had 1.34 (95% CI: 1.07, 1.49) times the odds of any neighboring joint pain compared to knees without thrust (**Table 4.2**).

**Table 4.2.** Odds of lower extremity joint pain in the presence of varus knee thrust.

<b>Pain Location</b>	<b>Varus Thrust Status</b>	<b>n/N*</b>	<b>Crude OR (95% CI)</b>	<b>p-Value</b>	<b>Adjusted† OR (95% CI)</b>	<b>p-Value</b>
<b>Individual Sites</b>						
<b>Low Back</b>	Present**	47/568	1.34 (0.89, 2.01)	0.17	1.47 (0.96, 2.24)	0.08
	Absent	51/807	1.00 (ref)	--	1.00 (ref)	--
<b>Hip</b>	Present	109/818	1.21 (0.94, 1.55)	0.14	<b>1.34</b> <b>(1.03, 1.73)</b>	<b>0.03</b>
	Absent	185/1714	1.00 (ref)	--	1.00 (ref)	--
<b>Ankle</b>	Present	78/888	1.22 (0.91, 1.63)	0.18	1.23 (0.91, 1.66)	0.19
	Absent	138/1887	1.00 (ref)	--	1.00 (ref)	--
<b>Foot</b>	Present	76/739	<b>1.55</b> <b>(1.16, 2.07)</b>	<b>0.003</b>	<b>1.60</b> <b>(1.18, 2.17)</b>	<b>0.002</b>
	Absent	112/1536	1.00 (ref)	--	1.00 (ref)	--
<b>Combined Regional Sites</b>						
<b>Proximal (Hip or Low Back)</b>	Present	148/1032	1.21 (0.98, 1.51)	0.08	<b>1.26</b> <b>(1.01, 1.58)</b>	<b>0.04</b>
	Absent	258/2246	1.00 (ref)	--	1.00 (ref)	--
<b>Distal (Ankle or Foot)</b>	Present	137/1032	<b>1.30</b> <b>(1.04, 1.63)</b>	<b>0.03</b>	<b>1.34</b> <b>(1.05, 1.68)</b>	<b>0.02</b>
	Absent	236/2246	1.00 (ref)	--	1.00 (ref)	--

**Table 4.2.** Odds of lower extremity joint pain in the presence of varus knee thrust.

<b>Pain Location</b>	<b>Varus Thrust Status</b>	<b>n/N*</b>	<b>Crude OR (95% CI)</b>	<b>p-Value</b>	<b>Adjusted† OR (95% CI)</b>	<b>p-Value</b>
<b>All Lower Extremity Pain</b>						
<b>Low Back, Hip, Ankle or Foot</b>	Present	251/1032	<b>1.27</b> <b>(1.07, 1.51)</b>	<b>0.01</b>	<b>1.34</b> <b>(1.11, 1.60)</b>	<b>0.002</b>
	Absent	454/2246	1.00 (ref)	--	1.00 (ref)	--

\*Limbs with Pain/Total Limbs or Persons with Pain/Total Persons, in the case of back pain

\*\*In at least one knee

†Adjusted for age, sex, race, BMI, and walking velocity.

## **DISCUSSION**

Previous studies examining the adverse structural and symptomatic effects of varus knee thrust have been restricted to the knee joint. To our knowledge, our study is the first to examine the effects of thrust on the risk of painful injury to neighboring joints along the lower extremity. Our findings suggest that thrust is associated with increased odds of incident frequent pain both proximal and distal to the knee joint.

The proposed likely mechanism for the relation of thrust to incident neighboring lower limb joint pain is that varus thrust has biomechanical effects along the kinematic chain of the lower extremity and leads to abnormal joint loads and moments at those joints. Varus thrust represents an abrupt abduction of the femur and adduction of the tibia, corresponding with hip abduction and ankle eversion; these motions may have implications for asymmetric loading of the hip and ankle joints. More removed sites such as the foot and low back may be affected due to compensations for this abnormal loading. In patients with knee OA, abnormal knee flexion was related to abnormal spine-pelvis-lower extremity alignment in the sagittal plane (Wang et al., 2016); it is likely that abnormal knee varus motion could affect lumbar spinal alignment in the frontal plane as well.

Of the two immediate neighboring joint sites (hip and ankle), statistically-significant increased odds of incident frequent pain were only observed at the hip. As malalignment of the tibia is known to affect contact area and subsequent clinical consequences at both the tibiotalar and subtalar joints (Tetsworth and Paley, 1994), increased odds of ankle pain would be expected. A low prevalence of self-reported ankle

pain (7.7%) could contribute to these results. The MOST sample is comprised primarily by individuals who self-identify as White or Black, with only 1.3% of the sample identifying as another race. Dunn et al. (2004) reported a significantly higher prevalence of ankle joint pain in Hispanic (44.7%) older adults compared to Non-Hispanic White (12.2%) or African-American (17.5%) individuals. Therefore, our results are not necessarily generalizable to all populations. Kraus et al. (2013) found a high prevalence of contralateral, but not ipsilateral, ankle and forefoot scintigraphic abnormalities in the presence of static knee malalignment. Our study only examined joints ipsilateral to the thrust knee; it is possible that thrust, a representation of dynamic knee malalignment, may affect risk of pain at the contralateral ankle.

Knee OA severity is related to changes in hip, knee, and ankle moments and other biomechanical parameters during gait (Aststephen et al., 2008). Patients with OA typically walk with substantially increased vertical loading rates, corresponding to greater axial loading rates at individual joints (Mündermann et al., 2005). As varus thrust is related to the progression of knee OA (Chang et al., 2004), knee OA may be an intermediate in the pathway between varus thrust and painful injury to these neighboring joints. For this reason, we did not include OA severity (measured as Kellgren-Lawrence grade) as a covariate in the analysis. Low numbers of incident pain cases precluded sensitivity analysis stratified by baseline OA status, as this would have decreased our sample size and limited our power to detect statistically-significant associations.

This study has several limitations. First, varus thrust was observed visually and quantitative analysis of joint angles and moments is therefore not possible. Nonetheless,

our method for detecting thrust yielded good test-retest reliability and is likely the method that would be employed in a clinical setting. Second, joint pain in this study is self-reported and therefore subjective. While participants were asked to report the presence of pain on most days of the past 30 days, there was no metric for pain severity. Third, it is not possible to know for certain whether pain reported at a certain joint was actually originating from that joint and not referred from elsewhere (Stupar et al., 2010). For instance, due to the deep location of the hip joint, diagnosing pain there can be difficult (Birrell et al., 2000). We attempted to circumvent this limitation by combining respective proximal and distal pain sites (e.g., to account for low back pain perceived at the hip or vice versa). This study only evaluated joint pain; it would be of interest to study structural damage to neighboring joints (e.g., hip OA) in the presence of thrust in the future.

In summary, our results indicate that the deleterious effects of varus knee thrust extend beyond the knee to neighboring joints, including the ankle/foot complex and the hip/low back complex. Varus thrust is potentially modifiable using non-invasive therapies, suggesting that targeting varus thrust may be beneficial in preventing frequent joint pain in older adults.

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**CHAPTER 5.**

**ANATOMICAL AND SENSORIMOTOR CORRELATES OF VARUS THRUST  
OBSERVED DURING GAIT: THE MULTICENTER OSTEOARTHRITIS  
STUDY**

## **ABSTRACT**

*Objective.* To determine the cross-sectional association of anatomical impairments (knee malalignment, knee laxity, leg length inequality, and foot posture) and sensorimotor impairments (muscle weakness and impaired joint position and vibration sense) with the prevalence of varus knee thrust in older adults with or at risk for knee OA.

*Methods.* Participants in the Multicenter Osteoarthritis (MOST) Study were evaluated for the impairments listed above using clinical and radiographic measures. Varus thrust was visually assessed from high-speed videos of forward walking trials. Logistic regression with generalized estimating equations was used to estimate the prevalence odds of thrust in categories of these impairments, adjusting for age, sex, body mass index, and walking velocity. For continuous variables, a test for linear trend in odds ratios was also performed.

*Results.* 1877 participants contributed 3730 knees. Thrust was observed in 31.3% of knees. Varus-aligned knees had 2.39 times the odds (95% CI: 1.96, 2.92) of varus thrust compared to neutral knees. Knees in limbs with supinated feet had 1.24 times (95% CI: 1.04, 1.45) the odds of thrust compared to feet with a neutral posture during gait. Knees with increasing static varus laxity had decreasing odds of varus thrust ( $p$  for trend = 0.0006).

*Conclusion.* Varus thrust is most prevalent in limbs with varus knees and supinated feet during gait. Varus knee laxity is protective against thrust in this population. Sensorimotor impairments are not associated with thrust prevalence in this

population. These results have implications for targeted interventions against varus thrust and subsequent medial knee damage.

## **INTRODUCTION**

Knee OA is the most common form of osteoarthritis and is a leading cause of disability and loss of quality-of-life in older adults. Knee OA occurs as a result of local mechanical risk factors in the context of systemic susceptibility. One mechanical risk factor for OA is knee thrust, a dynamic change in tibiofemoral joint alignment occurring during the mid-stance phase of gait. Knee thrust can occur in a varus (lateral) or valgus (medial) direction; however, varus thrust is more prevalent than valgus thrust among adults with or at risk for knee OA (Sosdian et al., 2016; Chang et al., 2013). Varus thrust has been associated with increased odds of medial tibiofemoral OA progression (Chang et al., 2004), medial tibiofemoral MRI-detected structural damage (Wink et al., 2017), and knee pain during weight bearing (Lo et al., 2012).

Given the strong putative association of thrust with knee OA progression, determining the underlying causes of varus thrust could facilitate the development of preventative strategies. In the Osteoarthritis Initiative cohort, Chang et al. (2010) identified several factors associated with the prevalence of varus thrust in individuals with and without OA. In persons without OA, greater age, body mass index (BMI), and varus malalignment were associated with the presence of varus thrust, while being African American, being a woman, and having greater knee extensor strength were protective against thrust. In those with OA, greater medial joint space narrowing and

varus alignment were associated with thrust presence, and being African American and a woman were again protective against thrust (Chang et al., 2010).

Varus thrust ultimately represents a dynamic instability in the knee joint during the stance phase of gait. During stance, an external knee adduction moment (KAM) acts around the knee joint, driving the knee into a varus position. This external moment is countered by an internal abduction torque that stabilizes the knee in the frontal plane. If there is an imbalance between these two torques (i.e., the internal torque was insufficient to counter the external KAM), a thrust may occur. The magnitude of the KAM is determined by the magnitude of the ground reaction force and the length of its perpendicular moment arm. Thrust may be a result of factors that increase one of these two components of the external KAM or factors that impair the knee's ability to counter the external KAM. We hypothesized that structural (anatomical) or sensorimotor (neuromuscular) impairments in the lower limb that could cause such an imbalance are associated with varus thrust. The aim of this study is to identify structural and/or sensorimotor impairments that are correlated with increased prevalence of varus knee thrust in older adults with or at risk for OA.

**Description of and Rationale for Anatomical Correlates of Thrust.** Thrust during walking could be related to structural abnormalities within the knee and lower extremity. Knee-based anatomical factors include knee malalignment and static ligamentous laxity. Leg length inequality or foot posture could also create a dynamic instability that results in a varus thrust.

*Static Knee Alignment.* Malalignment in the varus or valgus direction increases the loading on the medial or lateral compartment of the tibiofemoral joint, respectively, and this increase in loading is a risk factor for OA (Felson et al., 2013; Sharma et al., 2001; Yang et al., 2010). Previous studies suggested a possible relationship between alignment and thrust. Chang et al. (2004) found that over 80% of 67 knees with varus thrust were also varus-aligned on full-limb radiographs. Varus malalignment was also associated with significantly increased odds of varus thrust in knees with and without OA (Chang et al., 2010). In a study of 82 patients, Lo et al. (2012) found a significantly higher percentage of static varus alignment among the group with varus thrust (84%) compared to the group without (33%). Kuroyanagi et al. (2012) observed a statistically-significant ( $p = 0.0038$ ) positive correlation between the amount of varus thrust in degrees and the femorotibial angle in degrees. Mahmoudian et al. (2016) found a significantly-higher ( $p = 0.037$ ) magnitude of varus thrust in static varus knees compared to neutral knees after adjusting for age, height, and weight in female subjects. While not measuring thrust directly, Van der Esch et al. (2008), however, did not observe a correlation between skeletal alignment and varus-valgus position or range of motion during midstance.

*Static Knee Laxity.* Laxity, or instability of the knee joint, is thought to increase the risk of knee OA and contribute to its progression (Sharma et al., 1999a,b). Laxity is often associated with the ligamentous structures stabilizing the knee joint. In a sample of young adults (aged 16-48), Yoshimura et al. (2002) found that anterior cruciate ligament-insufficient knees had an increased lateral (varus) thrust pattern compared to normal

knees. Chang et al. (2010) speculated that instability resulting from stretching of the joint capsule and ligaments in malaligned knees would result in a thrust. Lo et al. (2012) also postulated that knees with greater knee laxity would have varus thrust, and Thienpont and Parvizi (2016) observed that varus alignment and lateral laxity are often present in knees with a varus thrust. Lewek et al. (2004) did not find an association between increased knee adduction moments (frequently associated with a varus thrust) in knee OA patients and lateral knee laxity. Van der Esch et al. (2008) did not observe a correlation between varus-valgus range of motion during gait and static knee laxity.

*Leg Length Inequality.* Leg length inequality is very common and can occur as a result of trauma or mild developmental abnormalities. Gait asymmetry resulting from leg length inequality has been widely reported; of note are findings that vertical ground reaction forces are larger in the longer limb (e.g., Bhave et al., 1999; Perttunen et al., 2004). Harvey et al. (2010) found that leg length inequality greater than 1 cm was associated with radiographic and symptomatic knee osteoarthritis, primarily in the shorter leg, proposing that this risk was due to differences in impact forces as a leg hits the ground, as well as differences in muscle lengths and consequent length-tension properties during stabilization.

*Foot Pronation/Supination.* Previous studies have shown that altering foot posture during gait using wedged shoe inserts alters lower limb biomechanics during gait (Ogata et al., 1997; Resende et al., 2015) and that the position of the foot center of pressure during gait is affected by dynamic knee alignment (Ferrigno et al., 2016). Increased foot pronation, or flat-footedness during gait is common among older adults as the arches of

the foot become lower with age (Hagedorn et al., 2013a). Gross et al. (2011) found that planus (flat) foot morphology was associated with a moderately increased prevalence of frequent knee pain and medial tibiofemoral cartilage damage. Excessive supination at the foot (in which an individual walks on the outer border of the foot) may be associated with excessive varus strain at the knee joint and medial tibiofemoral OA (Manoli and Graham, 2005).

### **Description of and Rationale for Sensorimotor Correlates of Thrust.**

Underlying sensorimotor or neuromuscular causes of varus thrust may include impairments in afferent input or efferent muscular function. The sensorimotor impairments hypothesized to be correlated with thrust included impairments in joint position and vibration sense and muscle weakness. Persons with these impairments may have difficulty stabilizing the knee during gait, due to either muscle weakness or diminished proprioceptive acuity, resulting in a thrust.

*Joint Position Sense and Vibration Sense.* Impaired proprioception, measured as joint position sense, has a cross-sectional relationship to the presence of knee pain and physical functional limitations (Felson et al., 2009), and persons with medial knee OA were shown to have impaired proprioceptive acuity in the varus direction (Chang et al., 2014); however, the temporal relationship between impaired proprioception and knee OA is not well understood (Segal et al., 2010a). Inability to sense the position of the joint during gait could potentially result in a dynamic instability or thrust; however, van der Esch et al. (2008) found no correlation between varus-valgus position during stance and joint proprioception. Chang et al. (2014), however, did find decreased varus-valgus

proprioceptive acuity in persons with medial knee OA who reported difficulty stabilizing the knee during gait. Joint position sense is often measured as a patient's ability to reproduce a pre-set joint angle; this method is questionable in terms of reliability as it may be confounded by disease severity, pain, delayed reflexes, and participant comprehension, concentration, and memory (Shakoor et al., 2017). Vibration perception is thought to be a more sensitive and objective proxy for joint position sense, as both senses are transmitted to the cerebral sensory cortex through the dorsal column of the spinal cord and medial lemniscus of the brainstem. This form of sensation may be important in providing tactile feedback to the central nervous system during walking (Shakoor et al., 2012). Deficits in vibratory sensation, demonstrated as an increased vibration perception threshold (VPT) were reported in individuals with knee and hip OA (Shakoor et al., 2008a,b), and vibratory sensation was shown to be correlated with the magnitude of joint loading (specifically, the external knee adduction moment) in persons with OA (Shakoor et al., 2012). This correlation was strongest at the site of the first metatarsophalangeal (MTP) joint, potentially due to its being the closest anatomic site to the ground during walking (Shakoor et al., 2012). Shakoor et al. (2017) found that in older adults with or at risk for OA, greater vibratory perception was associated with a decreased risk of incidence and worsening of knee buckling and showed a significant trend for protection against incident knee instability.

*Impaired Muscle Strength.* Quadriceps (knee extensor) weakness was shown to be a risk factor for symptomatic knee OA (Segal et al., 2009) as well as joint space narrowing in women (Segal et al., 2010b). Increased quadriceps strength, however, is

associated with an increased risk of knee OA in malaligned or unstable knees due to increased joint reaction forces (Sharma et al., 2003). Quadriceps weakness is thought to impair muscular stabilization of the knee, and this could result in a knee thrust. Chang et al. (2010) found a slight (adjusted OR: 0.96; 95% CI: 0.94, 0.99) protective effect of knee extensor strength against varus knee thrust in knees without radiographic OA but found no significant effects on varus thrust on knees with radiographic OA and no effects on valgus thrust. Similarly, Baert et al. (2013) found no relationship between quadriceps weakness and the knee adduction moment, a measure of medial knee loading that is frequently associated with varus thrust. Shakoor et al. (2017) showed that greater quadriceps strength was strongly protective against incident and worsening symptoms of knee instability, including sensations of shifting or slipping and knee buckling.

We leveraged the resources of the Multicenter Osteoarthritis (MOST) Study to ascertain cross-sectional relationships between these structural and sensorimotor impairments to varus knee thrust in older adults with or at risk for OA. We hypothesized that varus thrust is most prevalent in knees with potentially modifiable sensorimotor and structural impairments.

## **METHODS**

**Sample.** The Multicenter Osteoarthritis Study (MOST) is a prospective, observational cohort study of knee OA in older Americans that have OA or are at an increased risk of developing it. Factors considered to contribute to an increased risk of knee OA included being overweight, having knee symptoms without radiographic OA, and having a prior knee injury or previous knee surgery. Subjects were recruited from

two communities: Birmingham, Alabama, and Iowa City, Iowa. The MOST protocol was approved by the Institutional Review Boards at the University of Iowa; University of Alabama, Birmingham; University of California, San Francisco; and Boston University. Details of the MOST sample, including exclusion criteria, are described elsewhere (Segal et al., 2013).

Gait data were collected from 2,768 participants at the MOST 60-month clinic visit. Participants were instructed to walk across a 4.9-meter pressure-sensitive gait carpet, during repeated trials at a self-selected normal and a more hurried pace. A high-speed (60 Hz) video camera positioned at one end of the walkway recorded each subject's gait pattern. GAITRite resident software (GAITRite Inc., Clifton, NJ, <http://www.gaitrite.com>) was used to compute spatiotemporal gait parameters such as walking velocity.

MOST participants in the 60-month gait exam had to be able to walk independently over short indoor distances without the use of a walking aid or orthotic knee brace. Participants with recent (< 6 weeks) lower limb injury resulting in restricted weight bearing for over one week, recent hospitalization for a cardiovascular or respiratory disorder, lower limb amputation proximal to the toes, or difficulty walking because of a neurological condition were excluded.

**Assessment of Varus Knee Thrust.** A single trained observer, blinded to knee disease status, assessed thrust from high-speed videos of participants in the MOST 60-month gait exam during two self-paced walking trials. Participants dressed in short pants and their customary shoes. Skin markers were placed over the centers of the patellae and

tibial tuberosities to facilitate visualization of the knee. Knees were excluded from the thrust assessment if a clear view of either marker was obscured by clothing. Thrust was defined as the dynamic worsening or abrupt onset of varus alignment during the weight acceptance phase of gait, with a return to more neutral alignment during the lift-off and swing phases (Chang et al., 2010). Thrust was initially graded on a Likert-type scale as “definitely present,” “probably present,” “probably absent,” and “definitely absent.” Further, knees with thrust “definitely present” or “probably present” were further characterized as exhibiting thrust during “all steps,” “greater than half (but not all) of steps,” and “fewer than half of steps.” For the purposes of the current study, a simplified dichotomous variable was defined, wherein thrust was considered present when thrust was “definitely present” during any steps or “probably present” during “all steps.” Intra-rater reliability for varus thrust was substantial ( $\kappa = 0.73$ ).

**Assessment of Potential Correlates.** Potential structural and sensorimotor correlates at thrust were measured at various points throughout the course of the MOST study.

*Static Knee Alignment.* Static hip-knee-ankle (HKA) alignment was measured using full-limb anterior-posterior radiographs of each MOST participant, using previously-validated methods (Sharma et al., 2001). Participants stood with the tibial tuberosity facing forward. The x-ray beam was centered at the knee at a distance of 2.4 m. A setting of 100-300 mA/s and 80-90 kV was used, depending on limb size and tissue characteristics (Sharma et al., 2010). The HKA angle was defined as the angle formed by the intersection of a line from the center of the head of the femur to the center of the tibial

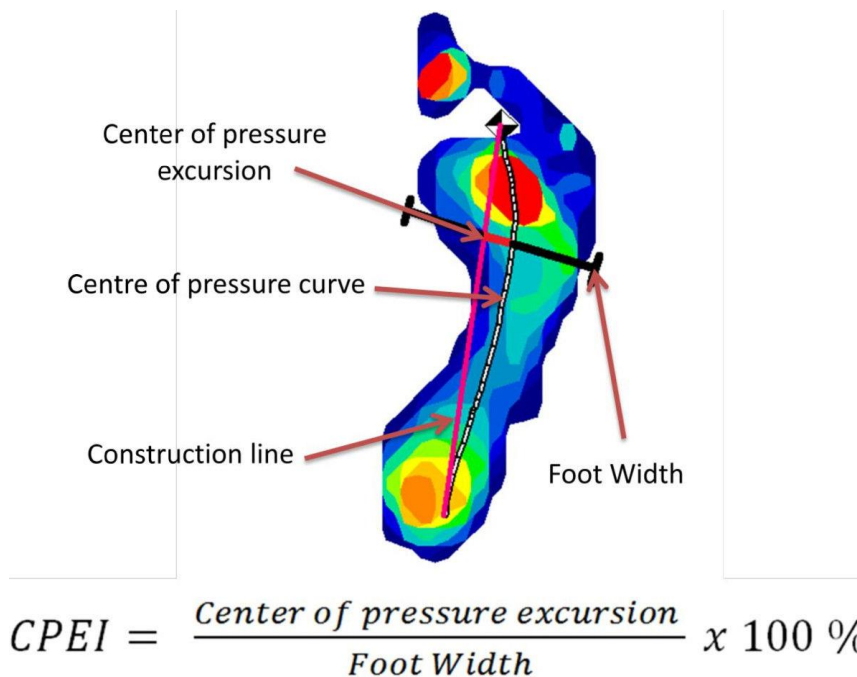
spines and a second line from the center of the talus to the center of the tibial spines. Inter-reader and intra-reader intraclass correlation coefficients (ICC) for HKA angle were 0.95 and 0.96, respectively (Sled et al., 2011).

*Static Knee Laxity.* Passive varus/valgus knee joint laxity was measured at the MOST baseline visit using the device and methods previously described by Sharma et al. (1999a,b). Briefly, participants sat on a bench with the thigh and ankle immobilized and the knee fixed at 20° of flexion; a hand-held dynamometer was used to standardize the load applied to the knee; and subjects' state of muscle contraction and relaxation was visually monitored. Laxity was measured in angular degrees following the application of 40 N in the varus or valgus direction. Reliability testing for this measure yielded ICC values ranging from 0.85-0.96 for within-sessions reliability and 0.84-0.90 for between-sessions reliability (Sharma et al., 1999).

*Leg Length Inequality.* Leg length was measured during the MOST baseline study visit from full-limb radiographs of each leg. Leg length was defined as the distance from the center of the femoral head to the most distal portion of the tibia directly over the talar dome not including the ankle joint. Intra- and interrater reliability of this measurement was high, with intraclass correlation coefficients of 0.96 and 0.97, respectively (Harvey et al., 2010).

*Foot Pronation/Supination.* Participants walked on a plantar pressure-measuring device (Emed, Novel Electronics) during the MOST 60-month plantar pressure exam. Foot biomechanics are described using the center of pressure excursion index (CPEI), averaged over five trials of walking at a self-selected speed (14-day test-retest

ICC = 0.82). The CPEI is the lateral displacement of the center of pressure curve from a line constructed between the initial and final centers of pressure values, normalized by the foot width at the anterior third of the foot (Song et al., 1996) (**Figure 5.1**). CPEI is used to measure dynamic foot function and can discriminate among planus, rectus, and cavus foot postures in the stance phase of gait: a lower CPEI indicates a more pronated/planus foot, while a higher CPEI indicates a more supinated/cavus foot.



**Figure 5.1.** Center of Pressure Excursion Index (CPEI). From Hagedorn et al. (2013a).

*Joint Position Sense.* Knee joint position sense was defined as the ability to reproduce a randomly-chosen knee flexion angle. At the baseline MOST clinic visit, each participant was blindfolded and instructed to sit with their legs hanging off the end of a raised chair with a view of their legs obstructed. A SG150 twin-axis electrogoniometer (Biometrics, Ladysmith, VA) was attached to the lateral aspect of the leg. Participants

were asked to extend their legs to a predetermined position, and then to reproduce the test position several seconds later. Proprioceptive acuity was operationally defined as the average error between preset and participant-reproduced knee flexion angles over ten trials (Felson et al., 2009; Segal et al., 2010a).

*Vibration Perception.* Vibration sense was measured as vibration perception threshold (VPT). VPT measures were obtained at the first MTP joint and at the tibial tuberosity during the MOST 60-month clinic visit using a biothesiometer (BioMedical Instruments) operating at frequency of 120 Hz. The voltage was initially set at 0 and then increased by 1 volt/second until the participant acknowledged sensation; this point was defined as the VPT. A higher VPT represents a greater sensory deficit. The average measurement of two trials was recorded (Shakoor et al., 2017). This method was reported to have good test-retest reliability, with ICC values ranging from 0.96 to 0.99 (Shakoor et al., 2008).

*Isokinetic Quadriceps Strength.* Knee extensor (quadriceps) strength measurements were also obtained at the MOST 60-month clinic visit. Knee extensor strength was defined as the maximal torque produced for each lower limb over four trials (Segal et al., 2009, 2010a,b), using a Cybex 350 computerized dynamometer (HUMAC software version 4.3.2/Cybex 300 for Windows 98; Avocent). Measurements were expressed in Newton-meters (Nm) and normalized to body size by dividing the maximum torque by the body mass index (BMI). The strength testing protocol had an ICC of 0.94, a co-effect of variation of 8%, and a within-subject variation of 6.3 Nm (Segal et al., 2009).

**Statistical Analysis.** Static knee alignment was defined as varus ( $HKA < 179^\circ$ ), neutral ( $179^\circ \leq HKA \leq 181^\circ$ ), or valgus ( $HKA > 181^\circ$ ). Foot posture was defined following the method of Hagedorn et al. (2013b): we created quintile categories of CPEI and defined the bottom 20% of CPEI values as over-pronated and the top 20% as over-supinated. As such, within the MOST cohort, the cutoff values for CPEI were  $< 13.94$  (over-pronated)  $13.94-25.14$  (neutral, referent), and  $> 25.14$ , (over-supinated). Leg length inequality was defined for the reference leg as being greater than 2 cm shorter or longer than the contralateral leg, between 1 and 2 cm shorter or longer than the contralateral leg, or equal to (within 1 cm of) the contralateral leg. For the remaining impairments (laxity, joint position sense, vibration sense, isokinetic quadriceps strength), quartile categories of increasing exposure were created (quartiles for isokinetic quadriceps strength were sex-specific, as muscle strength differs between males and females). Separate logistic regression models were used to estimate the odds of varus thrust in increasing levels of each exposure, adjusting for age, sex, BMI, and walking velocity. In addition, for the continuous variables placed in quartile categories, a test for trend in increasing odds of thrust with increasing exposure was performed. Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC).

## **RESULTS**

1877 participants (age  $67.6 \pm 7.7$ , BMI  $30.5 \pm 5.9$ , 88.1% White, 60.5% female, 44.1% Alabama, 41.2% KL grade  $\geq 2$ ) contributed 3730 knees. Thrust was observed in 31.3% of knees, and 41.6% ( $n = 781$ ) of participants had thrust in at least one knee.

Person- and knee-based characteristics of those with and without thrust are listed in **Tables 5.1** and **5.2**, respectively.

**Table 5.1.** Person-based characteristics of study sample (n = 1877 participants).

	<b>With Varus Thrust* (n = 781)</b>	<b>Without Varus Thrust (n = 1096)</b>
<b>Age, years</b> (mean ± S.D.)	68.4 ± 7.8	67.0 ± 7.7
<b>Sex</b> (% Female)	49.3	68.4
<b>Racial Background</b>		
-White/Caucasian (%)	89.2	87.2
-Black/African American (%)	9.2	11.6
-Other (%)	1.2	1.5
<b>BMI, kg/m<sup>2</sup></b> (mean ± S.D.)	30.6 ± 5.7	30.4 ± 6.0
<b>Site</b> (% Alabama)	41.6	47.6

\*In at least one knee

**Table 5.2.** Knee-based characteristics of study sample (n = 3730 knees).

	<b>With Varus Thrust (n = 1167)</b>	<b>Without Varus Thrust (n = 2563)</b>
<b>Radiographic Tibiofemoral OA*</b> (%)	48.6	39.0
<b>Hip-Knee-Ankle Angle, degrees</b> (mean ± S.D.)	176.7 ± 4.0	179.1 ± 3.5

\*Defined as KL grade ≥ 2

The prevalence odds of thrust in the presence of structural and sensorimotor impairments are presented in **Tables 5.3** and **5.4**, respectively. Varus-aligned knees had 2.39 times the odds (95% CI: 1.96, 2.92) of prevalent varus thrust compared to neutral knees. Knees in limbs with supinated feet had 1.24 times (95% CI: 1.04, 1.45) the odds of thrust compared to feet with a neutral posture during gait. Knees with increasing static varus laxity had decreasing odds of varus thrust (p for trend = 0.0006). After adjusting for

covariates, leg length inequality, isokinetic quadriceps strength, joint position sense, and vibration perception at the knee and foot were not statistically-significantly associated with varus thrust prevalence.

**Table 5.3.** Odds of varus thrust in the presence of structural impairments.

<b>Static Knee Alignment</b>			
<b>Mechanical Angle</b> (Degrees)	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>160.0 - 178.9°</b> (Varus)	747/1839	2.54 (2.10, 3.08)*	2.39 (1.96, 2.92)*
<b>179.0 - 181.0°</b> (Neutral)	162/768	1.00 (ref)	1.00 (ref)
<b>181.1 - 195.4°</b> (Valgus)	131/720	0.86 (0.68, 1.10)	0.90 (0.70, 1.16)
<b>Foot Posture</b>			
<b>CPEI</b>	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>&lt; 13.94</b> (Pronated)	206/716	0.97 (0.83, 1.15)	1.05 (0.88, 1.25)
<b>13.99 - 25.14</b> (Neutral)	655/2169	1.00 (ref)	1.00 (ref)
<b>&gt; 25.14</b> (Supinated)	266/720	1.32 (1.11, 1.56)*	1.24 (1.04, 1.45)*
<b>Leg Length Inequality</b>			
<b>Length Relative to</b> <b>Contralateral Leg (cm)</b>	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>&gt; 2 cm Shorter</b>	7/17	1.54 (0.52, 3.86)	1.63 (0.61, 4.36)
<b>1-2 cm Shorter</b>	90/286	0.99 (0.76, 1.29)	1.04 (0.80, 1.37)
<b>Within 1 cm</b> (equal)	948/3003	1.00 (ref)	1.00 (ref)
<b>1-2 cm Longer</b>	74/261	0.87 (0.65, 1.14)	0.90 (0.68, 1.21)
<b>&gt; 2 cm Longer</b>	11/44	0.70 (0.40, 1.21)	0.71 (0.39, 1.28)

**Table 5.3.** Odds of varus thrust in the presence of structural impairments.

<b>Varus Knee Laxity</b>			
<b>Varus Excursion</b> (Degrees)	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>0.00 - 1.00°</b> (Least Lax)	432/1168	1.00 (ref)	1.00 (ref)
<b>1.25 - 2.00°</b>	265/905	0.73 (0.61, 0.87)*	0.74 (0.61, 0.89)*
<b>2.25 - 3.00°</b>	247/837	0.69 (0.57, 0.84)*	0.73 (0.60, 0.90)*
<b>3.25 - 11.00°</b> (Most Lax)	215/781	0.65 (0.54, 0.78)*	0.69 (0.56, 0.85)*
<b><i>p</i> for Trend</b>	---	<0.0001*	0.0006*

†Number of knees with thrust/Total number of knees analyzed

‡Adjusted for age, sex, BMI, and gait speed

\*Results are significant at the 0.05 level

**Table 5.4.** Odds of varus thrust in the presence of sensorimotor impairments.

<b>Isokinetic Quadriceps Strength (Sex-Specific Quartiles)</b>			
<b>Maximum Torque</b> (Nm)	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>F: 84 - 149 /M: 145 - 253</b> (Strongest)	142/474	1.00 (ref)	1.00 (ref)
<b>F: 68 - 83 /M: 117 - 144</b>	142/477	0.96 (0.73, 1.26)	0.87 (0.65, 1.16)
<b>F: 51 - 67/M: 91 - 115</b>	197/616	1.02 (0.80, 1.33)	0.78 (0.58, 1.05)
<b>F: 7 - 50/M: 9 - 90</b> (Weakest)	86/360	0.74 (0.55, 1.01)	0.74 (0.52, 1.05)
<b>p for Trend</b>	---	0.14	0.07
<b>Knee Joint Position Sense</b>			
<b>Average Error</b> (Degrees)	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>0.6 - 2.9°</b> (Least Deficit)	238/817	1.00 (ref)	1.00 (ref)
<b>3.0 - 3.9°</b>	242/780	1.09 (0.84, 1.43)	1.14 (0.87, 1.50)
<b>4.0 - 5.2°</b>	245/749	1.18 (0.91, 1.54)	1.17 (0.89, 1.54)
<b>5.3 - 13.8°</b> (Greatest Deficit)	252/774	1.18 (0.91, 1.53)	1.18 (0.90, 1.52)
<b>p for Trend</b>	---	0.19	0.25
<b>Vibration Perception - Tibial Tuberosity</b>			
<b>Perception Threshold</b> (Volts)	<b>n/N†</b>	<b>Crude OR</b> <b>(95% CI)</b>	<b>Adjusted OR‡</b> <b>(95% CI)</b>
<b>2.50 - 13.50</b> (Least Deficit)	207/805	1.00 (ref)	1.00 (ref)
<b>13.75 - 19.25</b>	244/811	1.22 (1.01, 1.49)*	1.12 (0.91, 1.37)
<b>19.50 - 28.75</b>	270/826	1.28 (1.05, 1.56)*	1.08 (0.88, 1.33)
<b>29.00 - 51.00</b> (Greatest Deficit)	330/818	1.63 (1.32, 1.98)*	1.17 (0.94, 1.46)
<b>p for Trend</b>	---	<0.0001*	0.24

**Table 5.4.** Odds of varus thrust in the presence of sensorimotor impairments.

<b>Vibration Perception - 1<sup>st</sup> MTP Joint</b>			
<b>Perception Threshold (Volts)</b>	<b>n/N<sup>†</sup></b>	<b>Crude OR (95% CI)</b>	<b>Adjusted OR<sup>‡</sup> (95% CI)</b>
<b>1.5 - 9.75</b> (Least Deficit)	205/859	1.00 (ref)	1.00 (ref)
<b>10.00 - 15.50</b>	245/890	1.13 (0.93, 1.37)	1.03 (0.84, 1.27)
<b>15.75 - 26.50</b>	302/879	1.45 (1.19, 1.77)*	1.18 (0.95, 1.46)
<b>26.625 - 51.00</b> (Greatest Deficit)	337/876	1.68 (1.36, 2.08)*	1.15 (0.91, 1.47)
<b><i>p</i> for Trend</b>	---	<0.0001*	0.31

<sup>†</sup>Number of knees with thrust/Total number of knees analyzed

<sup>‡</sup>Adjusted for age, sex, BMI, and gait speed

\*Results are significant at the 0.05 level

## DISCUSSION

The results of this study demonstrate that varus knee thrust is most prevalent in limbs with static varus knee alignment and supinated feet during gait, while static varus knee laxity is protective against varus thrust in this population. Sensorimotor impairments are not significantly associated with the prevalence of varus thrust in this population.

The two anatomical impairments correlated with an increased prevalence of thrust, static varus malalignment and foot supination, both affect the external KAM by increasing the length of the moment arm perpendicular to the ground reaction force (Levinger et al., 2013). In these cases, a varus thrust may result from the lower limb's inability to produce an internal torque sufficient to offset an increased external KAM.

The correlation of varus thrust with static varus malalignment is of clinical interest, as the combination of varus thrust and static varus malalignment has

consequences for knee health. Varus-aligned knees with thrust had over 3 times the odds of medial knee OA progression (Chang et al., 2004) and increased odds of incident and worsening bone marrow lesions and worsening cartilage loss (Wink et al., 2017) compared to varus-aligned knees without thrust. In a small sample of knee OA patients, Iijima et al. (2015) demonstrated that knees with both static and dynamic varus (thrust) had increased odds of knee pain during walking compared to knees with static varus alone. Interventions that target varus malalignment could also be used to prevent the occurrence of varus thrust (e.g., Noyes et al., 2000); though it is important to consider that varus malalignment may occur as a result of deformity at either the joint itself, the bone metaphysis, or the bone diaphysis (Thienpont and Parvizi, 2016). Whether deformities at each of these locations are equally associated with the prevalence of thrust is unclear.

In a study of normal and osteoarthritic knees, Ogata et al. (1997) showed that a valgus (lateral-wedge) insole reduced the amplitude of the first lateral acceleration peak in varus thrust gait. This is consistent with our finding that varus thrust is most prevalent in a supinated foot. Foot pronation occurs to dissipate impact forces by driving the knee toward a valgus, internally-rotated position; therefore, a less-pronated (i.e., supinated) foot would be more likely to move into varus during stance. Conversely, Hunt et al. (2012) did not observe a substantial reduction in either peak varus angle at mid-stance (i.e., thrust magnitude) or medial knee loads with the use of a lateral shoe wedge in a single subject with varus thrust.

It is surprising that increased varus knee laxity was protective against the presence of varus thrust in this population. This is contrary to the hypotheses of Chang et al. (2010), Lo et al. (2012), and others who speculated that a lax knee would exacerbate dynamic instability and result in a thrust. This relationship could be explained as reverse causation: persons with greater knee laxity may adjust their gait by co-contracting muscles to stabilize a lax knee (Lewek et al., 2004, 2005), which would minimize the appearance of a thrust during gait. As an alternative to knee laxity causing thrust, it has been postulated that patients with thrust would develop lateral collateral ligament laxity due to chronic stretching of the joint (Andriacchi, 1994; Lewek et al., 2004; Thienpont and Parvizi, 2016).

It is also important to note that there is a distinction between the mechanisms of static and dynamic joint stability. In the unloaded knee, stability is provided by the ligaments, joint capsule, and other soft tissues; in the weight-bearing state, stability is provided by interactions between ligaments and other soft tissues, the geometry and congruence of the joint surfaces (i.e., the condyles), and tibiofemoral contact forces generated by muscle activity and gravitational forces (Sharma et al., 1999a,b; Markolf et al., 1981). Conversely, under dynamic conditions, stability is provided by proprioceptive input and cortical awareness of stabilizing muscular structures (Sharma et al., 1999a,b). Based on this distinction, a direct correlation between static ligamentous laxity and varus thrust is not necessarily expected; however, our finding of a statistically-significant protective trend is noteworthy and warrants further exploration.

While we did not see a statistically-significant association between thrust and leg-length inequality in any direction, we do note that shorter legs have non-statistically-significant increased odds of thrust, while longer legs have non-significant decreased odds of thrust. Small numbers of persons with leg-length inequality of 1 cm or greater may have limited our power to detect statistically-significant associations, but these findings are consistent with those of Harvey et al. (2010), who found increased risk for radiographic OA progression in shorter legs. Vertical ground reaction forces have been shown to be lower in shorter limbs, which would, theoretically, result in a smaller external KAM; however, a potential association between a shorter limb and varus thrust may relate to other gait discrepancies in limbs of unequal length. In a study of pediatric patients (ranging from 11-18 years), Perttunen et al. (2003) found that foot center-of-pressure curves coursed more laterally in the shorter limb and more medially in the longer limb. A lateral displacement of foot center-of-pressure (i.e., supination) could explain a relationship between shorter limbs and thrust.

Our findings on the potential sensorimotor correlates of thrust differ from what would be expected based on the findings of Shakoor et al. (2017). Their study found that greater vibration perception and quadriceps strength were protective against symptoms of knee instability, defined as knee buckling or sensation of shifting or slipping. While we found a slight increase in the prevalence odds of thrust in the presence of higher VPT, these results were not statistically-significant after adjusting for covariates. While not reaching statistical significance, we even observed a trend ( $p = 0.07$ ) in the protective direction of decreased quadriceps strength against varus thrust. Perhaps the symptoms of

knee buckling, shifting, or slipping perceived by participants in Shakoor et al.'s (2017) study occur in a different plane from thrust. It is also worthy to clarify that Shakoor and colleagues assessed self-reported instability outcomes, rather than a visually-observed measure of instability. It is unclear whether persons with a varus thrust recognize the thrust or acknowledge it as a potential source of instability.

Previous investigators did not observe a protective effect of increased knee extensor strength against radiographic or symptomatic knee OA (Segal et al., 2009; Sharma et al., 2008). Furthermore, Sharma et al. (2008) found that in malaligned and lax knees, increased quadriceps strength was associated with increased likelihood of knee OA progression. OA patients exhibit increased co-contraction of medial knee joint muscles (e.g., vastus medialis, medial gastrocnemius) in an attempt to stabilize the medial knee joint, increasing compressive forces across the joint (Lewek et al., 2004).

The primary limitation of this study is its cross-sectional design. Thrust was only assessed at one time point in the MOST study and therefore we have no measure of incident thrust in the presence of these exposures; therefore, we cannot assume causation. This limitation could explain the surprising protective effect of laxity on the prevalence of thrust, as described above.

A second limitation is the non-quantitative measure by which thrust was assessed. Visual assessment of thrust is a useful technique for clinical settings without quantitative gait analysis equipment; however, it is not possible to accurately assess varus angles or measure joint moments. Various quantitative definitions of thrust have been presented in the literature (e.g., Hunt et al., 2011; Sossdian et al., 2016; Yoshimura et al., 2002). These

varying definitions may cause the thrust event to be interpreted differently across definitions and from visual observation. It is possible that the association of anatomical and sensorimotor impairments with thrust prevalence may differ across definitions of thrust. Furthermore, without these quantitative measures, our ability to test clinical interventions for thrust is limited.

The scope of anatomical and sensorimotor correlates of thrust in this study was determined by the available structural and sensorimotor data collected in the MOST study. The potential correlates described here are by no means an exhaustive list of the factors that could contribute to the occurrence of thrust. Furthermore, it is important to note that not all data was collected at the same time point. Laxity, leg length inequality, and joint position sense were measured at the MOST baseline visit, while thrust was assessed at the MOST 60-month visit. Any cross-sectional associations between these variables and thrust must be interpreted with caution.

It is possible that the relationships (or lack thereof) between anatomical or sensorimotor impairments and thrust are related to the methods by which these impairments were evaluated in the MOST study. A limitation of the method used for measuring laxity is the inability to define a neutral point (Sharma et al., 1999b). Lewek et al. (2004) addressed this limitation when measuring laxity radiographically; this method may be more valid than that employed in the MOST study. Additionally, laxity in MOST participants was measured with the knee in 20° of flexion, which may be a greater flexion angle than is achieved in the phase of stance in which thrust is observed (Heiden et al.,

2009); thus, stabilizing structures may behave differently in the laxity assessment than they do in the weight-acceptance phase of gait.

In this study, we used two assessments to measure proprioception: joint position sense and vibration perception. Sharma (1999) noted that clinical studies of proprioception are limited by varying test conditions; therefore these methods are not always assessing identical sets of receptors and neural pathways. The neural pathways assessed through joint position sense and VPT testing in the MOST study may not be the same proprioceptive pathways that prevent a knee from exhibiting a thrust. Vibration perception is transmitted through the dorsal column/medial lemniscus neural pathway; these neurons synapse with higher-order neurons in the ventral posterolateral nucleus of the thalamus and continue to the cerebral sensory cortex. The spinocerebellar pathway is another proprioceptive pathway that transmits unconscious limb-position and muscle sense to the cerebellum. As mentioned above, it is unknown whether knee thrust is a conscious or unconscious event. If thrust is unconscious, proprioceptive input to prevent it (assuming thrust is related to proprioception at all) may be transmitted through the spinocerebellar pathway, whose function may not be represented VPT or joint position reproduction tests.

For our study, joint position sense was measured as the average error between pre-set and reproduced angles over ten trials, similar to the approach of Segal et al. (2010b). Felson et al. (2009) instead chose to evaluate the maximum error of the ten trials due to expected variability in test results. This variability could explain the lack of an association between joint position sense and thrust. Further, joint position sense in the

MOST study was defined as the ability to reproduce joint angles in the sagittal plane (i.e., flexion and extension). As thrust is a symptom of frontal-plane neuromuscular instability, this measure of proprioception may not be appropriate. Chang et al. (2014) found that individuals with medial knee OA had impaired proprioceptive acuity in the varus direction as well as diminished ability to actively stabilize the knee in a non-weight-bearing setting.

Isokinetic quadriceps strength was measured as an absolute. It has been suggested that a more appropriate measure for muscle strength in OA patients may be the hamstring/quadriceps strength ratio (Segal et al., 2009). A measure of knee extensor strength relative to knee flexor strength would indicate the presence of a muscle imbalance, which may be a larger source of instability than an overall muscle weakness.

Another limitation to our measure of muscle strength in MOST is similar to a limitation of our joint position sense measure: the only available measure of strength is knee extensor (quadriceps) strength; however, the quadriceps primarily act in the stance phase of gait to control knee flexion in the sagittal plane, so their role in stabilizing the frontal plane motion of the knee is dubious. Bennell et al. (2015) showed that exercise interventions targeting quadriceps strength did not improve pain in persons with varus thrust. Chang et al. (2014) found that knee OA patients had decreased varus-valgus isometric muscle torque, suggesting that frontal plane muscle strength should be addressed in this population, and noting (importantly) that muscle torque output (i.e., strength) does not necessarily correspond to motor control.

Heiden et al. (2009) assessed motor control in OA patients and found increased activation of lateral lower limb muscles, such as the vastus lateralis, biceps femoris, and lateral gastrocnemius, compared to medial muscles (vastus medialis, semimembranosus, and medial gastrocnemius); they hypothesized that co-contraction of these muscles was a protective mechanism to stabilize the knee. It is therefore likely that neuromuscular instability leading to thrust would result from lateral muscles (Andriacchi, 1994); hip abductors (such as the tensor fasciae latae), that act to counter the external KAM; or hip adductors, which have been postulated to decrease varus deformity of the lower limb in medial OA patients (Schipplein and Andriacchi, 1991; Yamada et al., 2001).

Consistent with other studies of knee thrust (Chang et al., 2010, 2013; Sosdian et al., 2016), valgus thrust had a low (less than 1%) prevalence in the MOST cohort. Therefore, we were unable to determine correlates of valgus thrust in this study. We expect that the directional anatomical impairments studied here would affect the prevalence of valgus thrust in the opposite direction from varus thrust. For instance, valgus thrust may be most prevalent in valgus-aligned limbs, consistent with the findings of Chang et al. (2010). Ferrigno et al. (2016) found that when medial (valgus) thrust was implemented as a therapy to reduce medial joint loads, the foot center of pressure shifted medially, suggesting that limbs with pronated feet would have a higher prevalence of valgus thrust. Repeating this study with a larger sample enriched with knees with valgus thrust would be of interest.

Few studies have investigated the role of non-invasive therapies targeting varus knee thrust in order to prevent incident or worsening knee disease. These therapies have

included lateral shoe wedges (Hunt et al., 2011; Ogata et al., 1997); gait retraining (Hunt et al., 2011); valgus bracing of the knee (Pollo et al., 2002); and neuromuscular exercise (Bennell et al., 2015). Understanding the underlying causes of varus thrust is crucial to creating interventions for thrust; in other words, therapies to prevent thrust that target anatomical or sensorimotor impairments that are correlated with thrust are likely to be more effective than a random approach.

In summary, the purpose of this study was to determine anatomical and sensorimotor impairments that were associated with the prevalence of varus knee thrust in older adults with or at risk for OA. We found that static varus knee malalignment and foot supination during gait was associated with increased prevalence of varus thrust, and that increasing varus knee laxity were associated with a decreased prevalence of thrust. While causation cannot be determined in this study, these cross-sectional relationships will inform future longitudinal studies. It is important to consider factors associated with thrust when creating interventions against thrust and subsequent medial knee joint loads.

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**CHAPTER 6.**  
**CONCLUSIONS**

## **Summary of Findings**

The overall objectives of this work were to expand the current understanding of varus knee thrust as a risk factor for structural and symptomatic changes to the knee joint, to examine the biomechanical and clinical relevance of knee thrust in the context of the entire lower extremity, and to elucidate potential anatomical and sensorimotor factors associated with increased prevalence of varus knee thrust in older adults with or at risk for OA.

Varus knee thrust was previously understood to be a risk factor for the progression of radiographic medial knee OA (Chang et al., 2004). Our findings herein indicate that, in addition, thrust is associated with increased odds of worsening medial MRI-detected cartilage loss and incident and worsening medial bone marrow lesions (Wink et al., 2017). As MRI-detected measures of structural damage are more sensitive than conventional radiographic measures, this has important clinical implications for early detection and prevention of knee structural damage and OA. Moreover, the association of thrust with BML could provide insight into the mechanism between thrust and knee pain.

Previous cross-sectional studies previously linked varus thrust during walking to prevalent knee pain during weight-bearing (Fukutani et al., 2016; Iijima et al., 2015; Lo et al., 2012). Our longitudinal study demonstrated an association of varus thrust with incident and worsening WOMAC knee pain. Further, thrust was associated with worsening WOMAC knee pain during weight-bearing and non-weight-bearing activities, and independent of baseline radiographic OA status.

The effects of varus knee thrust beyond the knee (i.e., on neighboring lower limb joints) have heretofore not been examined. We therefore did this through a biomechanical analysis of a single subject with unilateral varus thrust and an epidemiological analysis of the association of knee thrust with incident low back, hip, ankle, and foot pain. Our biomechanical model, while limited in being a single-subject study, demonstrated differences in frontal plane joint angles and moments at the knee, hip, and ankle between the thrust limb and the asymptomatic limb. Through our clinical epidemiological study, we observed that varus thrust was associated with increased odds of incident self-reported frequent pain at sites both proximal and distal to the knee. The results of our longitudinal clinical study bolster the findings in our biomechanical analysis by suggesting a directionality to the relationship between thrust and lower extremity joint effects.

Previously, very few factors were reported to be associated with varus thrust during walking, and these were largely demographic factors, such as race, age, sex, and BMI (Chang et al., 2010). Thrust was also reported to be associated with varus malalignment, while increased quadriceps strength had a slight protective effect against varus thrust in persons without OA (Chang et al., 2010). Our study examined additional anatomic and sensorimotor impairments at the knee and lower limb that could be associated with an increased prevalence of thrust. Our findings suggested that thrust prevalence is associated with static varus malalignment and increased foot supination during gait. Additionally, we found a protective effect of static ligamentous laxity against thrust in MOST study participants. We did not observe statistically-significant associations between thrust and any of the sensorimotor impairments examined. While

this study is limited by its cross-sectional design, it provides interesting insight into targeted therapies to reduce varus knee thrust and subsequent joint injury.

## **Discussion**

This work fills substantial gaps in the narrative regarding the role of varus knee thrust in osteoarthritis development, not only from a clinical epidemiology perspective, but also from functional and structural anatomy perspectives. The clinical epidemiology relevance of varus thrust is clear, given its demonstrated relationship to OA, an impactful public health concern among older adults. Epidemiologic principals are necessary to describe the distribution of risk factors for the occurrence and progression of OA (Zhang and Jordan, 2010). Using a large cohort, our study estimated the odds of additional clinically-relevant knee and lower extremity outcomes related to thrust. This further informs clinicians of the utility of varus thrust, an event that can be easily detected visually, as an indicator of future painful joint problems.

Clinical intervention studies specifically targeting varus thrust are rare compared to studies that are generally focused on reducing medial knee loads. The few studies that did aim to reduce varus thrust through non-surgical means (e.g., Hunt et al., 2011; Ogata et al., 1996) leveraged strategies for reducing medial loads (e.g., wedged insoles, gait modifications, orthotics), failing to consider the anatomical basis for varus thrust. It is therefore unsurprising that these interventions varied in success. Understanding the structural and functional anatomy of the knee and lower limb during gait is crucial to understanding how and why thrust occurs. Our study has begun to elucidate these relationships, albeit at a cross-sectional level. Furthermore, it is crucial to acknowledge

the knee joint as only one anatomic component within a chain of multiple joints and segments and consider that abnormal knee movement during gait is likely to have adverse effects along the entire lower limb.

Chapters 4 and 5 of this work place knee thrust into a larger biomechanical and anatomical context. One novel aspect of this study is the association of varus knee thrust with functional anatomy and painful injury at the ankle and foot. We found that knee thrust has a cross-sectional association with foot supination during gait and increased ankle eversion, accompanied by an increased and prolonged external ankle eversion moment, during stance. Whether thrust is a cause or consequence of these altered foot and ankle mechanics cannot be confirmed based on these cross-sectional data; however, we also found a longitudinal association between thrust and incident frequent foot or ankle pain. This longitudinal relationship provides some insight into the directionality of the relationship between thrust and the distal joints; nonetheless, this relationship is complex<sup>5</sup> and warrants further exploration.

### **Future Directions**

As mentioned above, the link between varus knee thrust and incident and worsening BML may explain the relationship of thrust to knee pain, as BML are thought to be the source of pain in knee OA (Felson et al., 2001). Future analyses should investigate whether BML presence and/or severity modifies the relationship between varus thrust and WOMAC knee pain.

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<sup>5</sup> For example, an overly-supinated foot is also associated with painful foot conditions, such as plantar fasciitis (Manoli and Graham, 2005). The co-occurrence of foot supination and thrust may explain the relationship between thrust and foot pain.

The use of a biomechanical model to depict thrust is an interesting concept, and while this work was limited in its scope, it provides a foundation for future research. Future work with a biomechanical model would leverage a larger sample designed with consideration of subject OA and thrust status. Future biomechanical study could also attempt to validate visual observation methods of thrust with kinematic and kinetic data, similar to the method of Chang et al. (2013).

A major limitation to this work is that varus thrust was only assessed at one time point within the MOST study. It would be of great interest to complete this assessment a second time in order to obtain data on incident varus knee thrust. This would allow longitudinal studies of anatomical and sensorimotor causes (as opposed to cross-sectional correlates) of thrust.

As mentioned in Chapter 5, the anatomical and sensorimotor correlates of thrust studied are not an all-encompassing list of features that could cause, or be associated with a higher prevalence of, thrust. Future studies, combined with longitudinal data on thrust, should systematically target the lower extremity anatomy as it relates to thrust at individual joint and segment, as well as whole-limb, levels. Additional anatomical correlates that could be considered in a future study include shape of the femoral and tibial condyles (Andriacchi, 1994; Duffell et al., 2017) and hip morphology. Moreover, anatomical and sensorimotor testing procedures should focus specifically on the frontal plane.

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