SEX DIFFERENCES IN LOWER LIMB MUSCLE ACTIVATION PATTERNS IN PARTICIPANTS WITH KNEE OSTEOARTHRITIS AND HEALTHY CONTROLS

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List of Acronyms

ϕ	Mean direction of muscle magnitude	MANOVA	Multivariate Analysis of Variance
ACL	Anterior Cruciate Ligament	MG	Medial Gastrocnemius
ADLs	Activities of daily living	MOA	Males with Osteoarthritis
AMI	Arthrogenous Muscle Inhibition	MOC	Male Older Controls
		MVIC	Maximum Voluntary Isometric Contraction
ANOVA	Analysis of Variance		
BF	Biceps Femoris	OA	(Knee) Osteoarthritis
BMI	Body Mass Index	SD	Standard Deviation
CI	Confidence Interval	SEM	Standard Error of the Mean
CCI	Cocontraction Index	SENIAM	Surface Electromyography for the Non-Invasive Assessment of Muscles
EMG	Electromyography		
EMG_i	Electromyography vector		
FITT	Frequency, Intensity, Type, Time	SI	Specificity Index
		Sports	Daily Living/Sports and recreation (KOOS)
FOA	Females with Osteoarthritis		
FOC	Female Older Controls	ST	Semitendinosus
GRF	Ground Reaction Force	TFL	Tensor Fascia Latae
ICC	Intra-Class Correlation	VL	Vastus Lateralis
KOOS	Knee Osteoarthritis and injury Outcome Score	VM	Vastus Medialis
		X_{EMG}	Mean magnitude of muscle activation
LG	Lateral Gastrocnemius		

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General Abstract

Muscular stabilisation strategies during activities of daily living alter in the presence of knee osteoarthritis (OA). By examining neuromuscular adaptations using our weight-bearing target match protocol, the main objective of this research is to establish sex differences in adaptations of neuromuscular control that are associated with older males and females with and without OA. 66 participants completed the protocol while EMG, ground reaction forces (GRF), and kinematics were recorded. Muscle activation patterns were presented in polar plots with an EMG vector representing normalised muscle activation in twelve directions, each representing a GRF vector scaled to 30% maximal effort. Asymmetry about the polar plot (activation occurring in one direction more than another) was determined and specificity index (SI) and mean direction of activation were calculated when appropriate.

Healthy females demonstrated greater rectus femoris (RF) mean muscle magnitude (X_{EMG}) ($p=0.067$) and less biceps femoris (BF) X_{EMG} than healthy males ($p=0.084$) and females with OA ($p=0.041$), and males and females with OA demonstrated greater RF X_{EMG} than healthy controls of the same sex ($p=0.016$, 0.072, respectively). Females with OA had significantly greater medial gastrocnemius X_{EMG} than healthy females ($p=0.031$) and males with OA ($p=0.020$). Females with OA have less specificity in all muscles compared to males with OA and OA participants generally had less specificity compared to healthy controls of the same sex. Healthy males had the largest SI for lateral gastrocnemius with an asymmetrical activation pattern contrasting the more symmetrical activation pattern of all other groups.

In conclusion, we suggest OA-affected adults and healthy females use a quadriceps dominant strategy to stabilise the joint, and that this strategy may be a compensatory mechanism for reduced quadriceps function. We suggest RF, BF, MG, and LG should be targeted for prophylactic intervention as they displayed altered activation strategies in participants with OA and healthy females.

1. INTRODUCTION

Arthritis is one of the most common chronic conditions in Canada and is a leading cause of pain, physical disability, and use of health care services (Arthritis Alliance of Canada, 2011). Osteoarthritis (OA) is the most common type of arthritis in Canada affecting 1 in 8 Canadians (Arthritis Alliance of Canada, 2011), and is most prevalent in the knee joint (Buckwalter et al., 2001). It is a progressive musculoskeletal disorder characterized by gradual loss of articular cartilage (Tanna, 2004) and bony growths (Kellgren & Lawrence, 1957).

In 2011, it was estimated that 4.4 million Canadians were living with OA and if the current trend continues, it is predicted that over 10 million Canadians (1 in 4) will have OA by 2040 (Arthritis Alliance of Canada, 2011). It is clear that OA has a significant impact on the Canadian economy: approximately $27 billion accounted for direct and indirect costs associated with this condition in 2010 (Arthritis Alliance of Canada, 2011). Medication, visits to health care professionals, tests, hospitalizations, and loss to the economy in public and private sectors account for the majority of these costs (Arthritis Alliance of Canada, 2011). This economic burden will continue to increase with the rise in prevalence, as well as the negative effect of decreased productivity and higher levels of self-reported disability that have been reported in people with OA (Heiden et al., 2009a).

A number of risk factors associated with the development of OA are leading to this increase in prevalence and economic burden. Non-modifiable risk factors include age and sex. OA can develop in people at any age, however approximately 89% of people affected with OA are over the age of 45 (Statistics Canada, 2012). The Arthritis Alliance of Canada (2011) reported approximately 48% of new OA cases were over the age of 60

in 2010 and if current trends continue that will increase to 53% by 2040. With the aging Canadian population, OA's impact on society will be significantly increased. Of the newly reported cases of OA, women have a higher prevalence then men (Arthritis Alliance Canada, 2011). This has been a trend and nearly two-thirds of all those affected are woman (Gariepy et al., 2009). Obesity is another risk factor with individuals having a BMI $\geq$30 kg/m^2 presenting an increased risk of OA development (Holliday et al., 2011; Felson et al., 1997). Those who become overweight earlier in adulthood may have a higher risk of developing hip and knee OA due to greater loading on weight-bearing joints for a prolonged period of time (Holliday et al., 2011). Almost 60% of those with OA who responded to the Canadian Community Health Survey (cycle 3.1) had a BMI classification of overweight or greater (>25 kg/m^2) (Gariepy et al., 2009). While higher BMI generally includes an increase in muscle mass, a decline in lower limb strength in females is associated with aging and has been suggested as a risk factor in females for developing OA (Holliday et al., 2011; Felson et al., 1997; Segal et al., 2010). This strength decline may reduce joint stability increasing the risk of injury and joint damage. Further research examining sex differences at the neuromuscular level to describe the adaptations utilised by each sex in a healthy and OA aging population is merited to determine what, if any, adaptations coincide with joint degeneration.

Purpose and Research Question

OA's negative impact on Canada is continuing to grow, warranting further research to uncover neuromuscular control adaptations associated with preserving the

integrity of joint structures. By examining fundamental knee joint stabilisation strategies associated with this condition, we hope to produce data that will eventually enhance rehabilitation programs, reducing the negative effects this condition has on affected individuals and subsequently society. As there is a greater prevalence of OA in females, and muscles affect joint loading and stability, investigation of sex differences in muscle activation and stabilisation strategies may provide valuable insight into the cause of the increased risk of joint degeneration in females. Therefore, the general research question for this thesis is: What adaptations in neuromuscular control are associated with OA in males and females over the age of 50? To answer this general question, the primary aims of this thesis are to:

Aim 1: Investigate sex differences in knee joint stabilisation strategies and to identify each muscle's role in joint stabilisation in older, healthy adults during highly-controlled, direction-dependent loading.

Aim 2: Investigate sex differences in lower limb muscular activation patterns and determine muscle stabilisation roles associated older adults diagnosed with knee osteoarthritis.

Aim 3: Investigate knee extensor and knee flexor activation inhibition in older males and females with and without knee osteoarthritis through a ratio of a scaled voluntary *experimental* peak torque production versus the model output *ideal* peak torque production.

Relevancy

Joint instability is commonly reported in older adults and to a greater degree in

people affected with knee osteoarthritis. Muscular activation strategies to stabilise the knee joint have been shown to differ between younger males and females (Flaxman et al., 2014). With age, these strategies may continue to change in response to reduced muscle mass and strength to maintain joint stability. Specifically, neuromuscular adaptations, such as reduced muscle function, increased cocontraction (Hortobagyi et al., 2005), muscle imbalance, and increased normalised muscle activation of the quadriceps and hamstrings (Hortobagyi & DeVita, 2000, Madhaven et al., 2009) may negatively alter joint loading making this population more susceptible to OA. It has been suggested that the strength decline seen in the aging population, specifically of the knee extensors, is a pre-cursor to degeneration of knee joint cartilage (Becker et al., 2004). By comparing muscular strength and the resulting stabilisation strategies between the sexes in older adults with and without OA, further insight into the cause of greater prevalence in females were suggested to be uncovered. We suggest healthy males will set the gold standard for strategies that reduce risk of OA development while OA-affected males will demonstrate strategies to stabilise the joint in response to cartilage degeneration; however, as this is a cohort study, cause-and-effect will not be determined. Strategies utilized by healthy females cannot be considered a gold standard as our control subjects were not age matched and the majority of them were in their 50's (9/17) whereas the majority of OA-affected females were in their 60's (10/14). This research will provide insight to the relationship between neuromuscular adaptations of muscles, which provide stability to the knee, and how their roles change between males and females with and without OA.

This research is part of a long-term research project designed to compare

neuromuscular control strategies of young, old, and OA-affected males and females. Neuromuscular activation strategies used by participants were investigated during a highly controlled, isometric, weight-bearing target match protocol at various anterior-posterior-varus-valgus positions with force loads scaled to 30% of their maximum ground reaction forces (GRF). The primary goal to identify neuromuscular adaptations associated with aging and OA determined some of the neuromuscular deficits experienced by these populations and provided insight into the impact joint degeneration has on muscular joint stabilisation strategies.

Review of Literature

Osteoarthritis: Cartilage Degeneration

Radiographically, features of OA include: formation of osteophytes on the tibial spines, periartciular ossicles, narrowing of joint cartilage, small pseudo cystic areas with sclerotic walls, and altered shape of the bone ends (Kellgren & Lawrence, 1957). These features reduce joint contact surfaces in the medial and/or lateral compartments, which may lead to altered muscle activation strategies as a mechanism to maintain joint stability. It has been suggested that altered muscle activation strategies lead to changes in joint loading further progressing degeneration of joint cartilage (Piscoya et al., 2005). Unfortunately, further degeneration can lead to increased pain, decreased mobility, and consequently, further muscle atrophy and strength declines (Glass et al., 2013; Segal et al., 2010). Those affected may continue to alter muscle activation strategies in response to these symptoms resulting in imbalanced joint loading, while others may establish a strategy that maintains their level of joint health and limits the progression of OA.

Altered Neuromuscular Function

Joint stability requires a complex interaction between neural control and the musculoskeletal system. This neuromuscular interaction adapts due to such things as injury, aging, or a chronic condition such as OA. Due to the high prevalence of OA in the elderly, it is important to establish the neuromuscular adaptations associated with aging alone to later determine which adaptations are specifically related to the onset and progression of OA.

Age-related Changes in Neuromuscular Function

Muscle Activity & Mobility

Aging is associated with an increase in normalised muscle activity (percentage of maximum voluntary isometric contraction) of the lower limb as well as natural atrophy (Madhavan et al., 2009). Compared to younger healthy counterparts, elderly people have greater normalised muscle activity of the lower limb during functional movements, such as the loading phase of a downward step (Hortobagyi & DeVita, 2000), as well as greater agonist activity during exercises such as a single-limb squat (Madhavan et al., 2009). This consensus that lower limb EMG activity increases with age suggests it is a neuromuscular adaptation to aging. While there is no known direct cause, it may be a compensatory mechanism used in response to a decrease in muscle strength, which is also associated with aging (Hortobagyi et al., 1995; Larsson & Karlsson, 1978; Larsson et al., 1979; Reid et al., 2012). As muscles are the power behind joint movement and aid in providing stability to the joint (Felson, 2004), it is important to investigate adaptations in

level of normalised muscle activation resulting from age-related changes to muscle physiology.

Exercise and mobility are other factors affecting muscle strength in the elderly. A lower maximum isometric torque combined with a decrease in cross-sectional area of type II fibres and slower movement speeds in the vastus lateralis has been reported in sedentary, older adults compared to older adults who participated in strength training regularly (Klitgaard et al., 1990). This suggests regular strength training can counteract age-related changes in muscle function and morphology. Decreased mobility is common in older populations (Daley & Spinks, 2000) and is linked to neuromuscular adaptations that affect the ability to perform activities of daily living with ease (Hubley-Kozey et al., 2006). Currently it is unknown which occurs first, however limited mobility in the elderly is associated with less peak muscle power, strength, cross-sectional area, and rate of neuromuscular activation when compared to mobile, elderly and healthy, younger controls (Reid et al., 2012). Thus, strength training and mobility are associated with the ability to generate maximum isometric torque.

Interestingly, during gait, while in general there is a greater relative net EMG amplitude from the quadriceps and hamstrings, there are altered contributions from muscles of the hip, knee, and ankle in the production of net support torque compared to younger adults (DeVita & Hortobagyi, 2000a). A decrease in plantar flexor and knee extensor torque along with an increase in net hip extensor torque summed to a similar net support torque found in younger controls. This provides evidence of age-related altered muscle roles being adapted to produce the same relative task.

Posture & Stiffness

This altered activation pattern seen in elderly populations during gait relates to the kinematic adaptations such as less relative time in swing phase, shorter stride length and a higher stride frequency (DeVita & Hortobagyi, 2000a). All of these factors contribute to less time in single-limb stance, which requires neuromuscular control for balance, and can be considered a safer movement strategy for the elderly (DeVita & Hortobagyi, 2000a). Furthermore, in this population lower limb muscle pre-activity's positive correlation with leg stiffness, determined by stress (maximum relative ground reaction force between ground impact and maximum knee flexion) over strain (maximal shortening of the distance between the fifth metatarsal head and hip joint between ground contact and maximal knee flexion), is a muscular adaptation also associated with an apparently safer movement strategy (Hortobagyi & DeVita, 2000). The increase in lower limb muscle pre-activity may pre-set muscle activation levels to anticipate impact with the ground (Hortobagyi & DeVita, 2000) while the increase in leg stiffness requires less muscular control to complete the movement (DeVita & Hortobagyi, 2000b). While increasing pre-activity to prepare for impact may seem beneficial, due to deficits in muscle strength and endurance, muscles may fatigue faster reducing the ability to absorb shock during impact. This may lead to increased joint loading further progressing OA. During downward stepping, when the height of the step was increased from 10% to 20% body height, the elderly did not increase their knee flexion to the same extent as the young adults (Hortobagyi & DeVita, 1999) suggesting the ability to adapt the neuromuscular system decreases as the motor challenge enhances. Reduced range-of-motion in the knee and ankle joints during downward stepping (Hortobagyi & DeVita, 1999) and gait (DeVita & Hortobagyi, 2000a) are postural adaptations that create a more

erect lower limb that is associated with leg stiffness and aging. All of these adaptations reflect a more cautious movement strategy increasing perceived stability for the elderly and those with OA. However, further research on the consequences this strategy has on joint structures is necessary.

Altered Neuromuscular Function in Osteoarthritic Individuals

Neuromuscular adaptations associated with aging alone tend to be exacerbated in the OA population. Adaptations such as increased levels of normalised muscle activation along with decreased strength, mobility, and perceived stability have been reported. Altered muscle contributions to provide stability to the joint affect loading of joint cartilage. Therefore, further investigation into the relationship between these adaptations and joint degeneration is vital to understanding the role muscles play in preventing and progressing OA.

Muscle Amplitude

Greater normalised EMG activation levels in various muscles crossing the knee joint has been reported in participants with OA compared to age-matched controls signifying neuromuscular control strategies adapt along with this condition (Schmitt & Rudolph, 2007; Heiden et al., 2009a). Studies examining the relationship of normalised EMG activation levels and moderate to severe OA have had conflicting results. Hubley-Kozey et al. (2009) and Rutherford et al. (2013) suggest severe OA coincides with greater quadriceps and hamstrings normalised EMG activity and slower gait speed compared to moderate severity and asymptomatic controls while Zeni et al. (2010) found significant differences in peak quadriceps and hamstrings EMG between moderate OA and controls,

but no significant difference between moderate and severe OA. However, people with moderate-severe OA appear to increase their muscle activity to compensate for decreased muscle strength, and possibly degradation of the joint due to decreased cartilage, when completing a dynamic task such as walking (Hubley-Kozey et al., 2009). Greater normalized activation and prolonged activation of the quadriceps and hamstrings have been associated with marked joint space narrowing, large osteophytes, and severe sclerosis in a Kellgren & Lawrence (K-L) grade IV OA group compared to asymptomatic and K-L grade II and III OA groups during gait (Rutherford et al., 2013). Heiden et al. (2009a) also found greater net normalized muscle activation in an OA group during gait, specifically during the loading and early stance phase. This corresponded with slower gait speed in females with knee OA. Vastus medialis (VM), vastus lateralis (VL), and lateral hamstring (LH) activation increased the greatest when compared to age-matched controls during midstance of gait (Schmitt & Rudolph, 2007).

While it has been shown quadriceps and hamstring muscle amplitude generally increases with the presence of OA, reports on the activity of the gastrocnemius muscles vary based on the movement. During walking, gastrocnemius amplitude reportedly decreases with the presence of OA (Hubley-Kozey et al., 2009) while during a lateral translation perturbation, medial gastrocnemius muscle activity increases with medial compartment OA, but not in age-matched controls (Lewek et al., 2005). This increase in medial gastrocnemius activity coincides with an increase in medial cocontraction of the quadriceps and hamstrings and therefore may be part of the stabilisation strategy required by people with OA to compensate for the lateral perturbation. Based on the above, we

can conclude that a general increase in muscle activity is commonly seen during activities of daily living in the OA population.

Muscle Weakness

The described general increase in muscle amplitude coincides with a decrease in quadriceps strength, muscle volume (Berger et al., 2012), and peak torque production (Rice et al., 2011). A decrease in muscle strength, an age-associated phenomenon, is associated with less muscle mass which has been seen alongside the first signs of joint degeneration: reddening and fibrillation of articular cartilage in rabbits (Herzog et al., 2003). Specifically, quadriceps weakness has been considered a risk factor for the onset of OA symptoms (Segal et al., 2010) and is commonly reported in the OA population (Heiden et al., 2009b; Lewek et al., 2004; Ramsey et al., 2007; Rudolph et al., 2007; Schmitt & Rudolph, 2007). Reported quadriceps weakness in males and females is partially due to arthrogenous muscle inhibition (AMI) (Hurley & Newham, 1993), the inability to recruit all motor units in the muscle group, resulting in poorer voluntary contraction of this major muscle group (Hurley et al., 1997; Lewek et al., 2004). Quadriceps dysfunction causes an imbalance in muscle strength about the knee joint increasing its joint laxity and thereby decreasing its stability and altering joint loading. This may contribute to cartilage degeneration linking it to the articular damage associated with OA (Hurley et al., 1997). In healthy older adults, lower quadriceps strength increased the risk of symptomatic OA and joint space narrowing in females and similarly, but to a lesser extent, in males (Segal et al., 2012). This inability for the quadriceps muscle to recruit all muscle fibres and the associated loss of muscle mass, strength, and

motor control may play an important role in the development and progression of joint degeneration (Herzog et al., 2003).

This situation can be altered, however, as Lewek et al. (2004) suggests adequate instruction, feedback, and allowing several attempts to reach maximum contraction can decrease activation failure thereby decreasing the level of AMI. Furthermore, following isometric, isokinetic, and individually prescribed exercise programs, quadriceps AMI decreased significantly and was statistically similar to the non-affected limb (Hurley & Newham, 1993). Isometric quadriceps strength increased causing subjective improvement in functional ability and confidence in the affected limb (Hurley & Newham, 1993) and following Hafez et al.'s (2013) twelve week quadriceps and hamstrings strengthening program, OA patients aged 50-65 had increased range-of-motion, and decreased perceived knee pain, limitation of functional performance, and stiffness. Sharma et al. (2003) reported higher knee extensor strength at baseline was associated with an increase in joint space narrowing (OA progression) at 18-month follow-up in patients with high knee joint laxity (>6.75deg) and valgus alignment. Unfortunately, they did not measure knee extensor strength at the 18-month follow-up suggesting further research on the impact of knee extensor strengthening on OA patients with valgus alignment and high knee joint laxity is required. Health-care practitioners aiding in the rehabilitation of OA should therefore assess their patient's alignment and knee extensor strength to determine if it is appropriate to utilise these strategies to achieve effective results in improving joint function and stability. Insight into the best intervention strategy is still needed in order to focus training on muscles with the greatest potential to improve joint health through modifications to muscular stabilisation strategies.

Cocontraction & Knee Adduction Moment

Cocontraction of agonist-antagonist muscles of the lower limb is a natural mechanism for neuromuscular control used in daily life. Hamstrings-quadriceps cocontraction is an activation pattern that can reduce anterior tibial displacement (Draganich et al., 1989) creating a more stable joint. Furthermore, cocontraction occurs during many weight-bearing activities of daily living and weight-bearing increases tibiofemoral contact force aiding in joint stabilisation (Markolf et al., 1981). Greater levels of cocontraction have been seen in older healthy adults compared to younger adults (Hortobagyi et al., 2005), as well as in OA populations compared to age-matched controls (Hubley-Kozey et al., 2009; Lewek et al., 2005; Metcalfe et al., 2013; Schmitt & Rudolph, 2007; Zeni et al., 2010). This may be an adaptation to compensate for the decrease in joint stability due to joint degeneration and decreased muscle strength associated with the condition. Further examination of cocontraction as a neuromuscular strategy in OA suggests lateral site cocontraction increases throughout the progression of OA (Hubley-Kozey et al., 2009). While this may be a strategy to unload the commonly affected medial compartment, it consequently results in higher levels of tibiofemoral forces (Lu et al., 1997). Unfortunately, this altered loading environment may facilitate the degradation of articular cartilage, progressing OA (Metcalfe et al., 2013; Piscoya et al., 2005). When examining medial knee OA muscular activation strategies, greater medial cocontraction of the quadriceps-hamstring and quadriceps-gastrocnemius occurs during standing, lateral translation on a plate (Lewek et al., 2005), and walking (Schmitt & Rudolph, 2007). Increased levels of cocontraction reported in moderate to severe OA compared to healthy controls is partially due to an increased level of antagonist

activation, reflecting an internal strategy to maximize stability during walking (Zeni et al., 2010). Along with greater cocontraction, higher knee adduction moments compared to controls occur during gait (Astephen et al., 2011; Heiden et al., 2009a; Metcalfe et al., 2013; Rudolph et al., 2007; Schmitt & Rudolph, 2007). Miyazaki et al. (2002), reported a positive correlation between baseline knee adduction moment and six-year follow up of joint space narrowing and a negative correlation with medial joint space and pain. The risk of OA progression increased 6.46 times with a 1% increase in knee adduction moment. Therefore, while the OA population may adapt these mechanisms to increase leg stiffness leading to perceived stability, these adaptations may be detrimental to the joint by increasing the joint load (Lewek et al., 2005) and decreasing medial joint space (Miyazaki et al., 2002). Stiffening of the knee occurs with a high cocontraction index (CCI) and smaller knee flexion range of motion (Schmitt & Rudolph, 2007). While perceived stability positively correlates with CCI (Lewek et al., 2005), the effect on long-term joint integrity continues to be investigated. Higher CCI and reduced knee joint range-of-motion may result in higher joint compression and greater contact forces and with reduced surface area of cartilage to dissipate these forces, the increased CCI and reduced range-of-motion could exacerbate joint destruction further progressing OA (Lewek et al., 2005). Further research investigating the impact this stiffening strategy has on joint loading during dynamic and isometric tasks is warranted to determine if it is beneficial or harmful to joint integrity.

Stability in the Active and Passive Knee Joint

Studies investigating knee joint stabilisation strategies in healthy populations have examined sex-related differences in joint laxity, muscle strength, and EMG amplitude.

Sex-related Differences in Joint Laxity

Females have less knee joint stability when it is examined as a measure of joint laxity (Huston & Wojtys, 1996; Pollard et al., 2006; Rozzi et al., 1999; Shultz et al., 2012). Greater laxity in the joint, determined by an arthrometre measurement of anterior tibial translation, decreases the level of joint stability. Compared to male athletes, females, controls and athletes, had greater knee joint laxity during anterior tibial translation stress tests (Huston & Wojtys, 1996). While a difference in lower extremity lean mass seen between males and females has been associated with the level of joint laxity in the frontal and transverse planes (Shultz et al., 2012) it is unclear if males' greater lower extremity lean mass is the cause of their increased joint stability. Factors such as body mass and height (Rozzi et al., 1999) have not been found to affect joint laxity. Imbalanced agonist-antagonist muscle strength may influence laxity in the joint and lead to altered EMG amplitudes to compensate and increase stability. In females, excessive joint laxity resulting in a reduced ability to rely on ligamentous structures has resulted in increased hamstring activity during a drop landing to achieve functional joint stabilisation (Rozzi et al., 1999). This neuromuscular adaptation of increasing muscular activation to compensate for the reduced muscle strength and increased joint laxity may be a strategy to increase joint stability in response to the demands of a movement and requires further investigation.

Muscle Strength & EMG Amplitude

Females have statistically weaker quadriceps and hamstring muscle strength measured during maximum isokinetic contractions, even when normalised to body weight (Huston & Wojtys, 1996). This lower strength reportedly increased the risk of worsening knee pain (Glass et al., 2013), increased joint space narrowing, and decreased function abilities (Segal et al., 2010). In a study investigating the relationship between quadriceps strength and joint space narrowing with a baseline and 30-month follow-up, Segal et al. (2010) reported females, but not males, with quadriceps weakness had a significantly increased risk of joint space narrowing progressing OA severity. Also, females with OA generally have less quadriceps muscle volume and lower peak knee extensor torque (normalised to muscle volume) than males with OA (Berger et al., 2012). While muscle volume explained part of the significant difference in absolute peak torque, previous studies suggest quadriceps strength has a greater effect on the development OA in females than in males (Segal et al., 2010; Slemenda et al., 1998). Furthermore, quadriceps-hamstrings strength imbalance in females results in altered muscle activation such as significantly lower hamstring pre-activity prior to side-cutting (Bencke & Zebis, 2011) and greater quadriceps activation during the extension phase of a single-limb squat (Youdas et al., 2007). While females exhibited approximately 20% greater normalised rectus femoris EMG activity than hamstrings, males exhibited a more balanced hamstring-rectus femoris normalised EMG activity (approximately 5% greater hamstring activity) (Youdas et al., 2007). Decreased hamstring activation relative to quadriceps activation is commonly seen in females and results in a lower hamstring-quadriceps cocontraction ratio which has been implicated as a potential risk factor for lower extremity injury as it increases anterior tibial shear force (Beynnon et al., 1997). This

imbalance can be associated with greater joint laxity and furthermore decreased joint stability in females. This allows a greater tibial shear force during movement (Beynnon et al., 1997) that can be detrimental to joint cartilage and progress OA.

Females also exhibit kinematic adaptations of the lower limb corresponding to their altered muscle activation patterns. These include: smaller peak knee flexion angle, larger peak hip extension angle, and smaller peak hip flexion angle, creating a more erect body posture during a single-limb squat (Dwyer et al., 2010; Graci et al., 2012). The altered muscle activation patterns corresponding with these kinematic changes that are commonly exhibited by females may be a compensatory mechanism for strength deficits and increased joint laxity and may ultimately lead to the greater prevalence of OA in this sex.

Knee Osteoarthritis and injury Outcome Survey (KOOS) Ratings in Older, Healthy and OA Populations

The KOOS rates symptoms, pain, function/activities of daily living (ADL), function/sports and recreation (sports), and quality of life (QoL) on a Likert scale of 0-4. Scores were converted to a scale of 0-100 (worst-best) (Roos et al. 1998). Previous studies have used the KOOS as an effective evaluation tool for people with knee osteoarthritis (Kumar et al., 2013; Lohmander et al., 2004; Roos & Lohmander, 2003; Van Porat et al., 2004). Average KOOS ratings have varied between studies, but all show significantly lower scores for all five subscales compared to controls and generally have a negative correlation with age in OA populations. Von Porat et al. (2004) reported average ratings of 85, 73, 91, 64, and 61 for subscales pain, symptoms, ADL, sports, and QoL,

respectively, in a knee osteoarthritis population aged 32-53. Kumar et al. (2013) reported lower average ratings of 64.2, 62.3, 71.6, 42.2, and 41 in an older OA group with a mean (standard deviation (SD)) age of 65.2 (9.5). Average ratings varied from 96, 94, 96, 90, and 92 in a healthy population aged 36-79 (Von Porat et al., 2004) to 98.5, 99.8, 100, 96.7, and 99 for controls aged mean (SD) 59.5 (10.4) (Kumar et al., 2013). KOOS cut-off values used to define symptomatic OA are: pain ≤86.1, symptoms ≤85.7, ADL ≤86.6, sports ≤85 and QoL ≤87.5 (Lohmander et al., 2004). Based on these findings, KOOS would appear to be a valid tool for classifying OA-affected populations.

A Reductionist Approach to Evaluation of Neuromuscular Control

Isometric Muscle Activation at the Knee

As previously described, investigating muscle stabilisation strategies during dynamic tasks such as gait, single-limb squats, and downward stepping can provide conflicting results. While loading is generally examined during flexion and extension of the knee, it is important to acknowledge that the knee can be loaded in any direction during functional activities. Previous studies have investigated muscle stabilisation strategies about the knee during varus and valgus isometric loading in healthy participants using a non-weight-bearing protocol (Buchanan & Lloyd, 1997; Krishnan et al., 2008; Lloyd & Buchanan, 2001; Lloyd et al., 2005).

The major limitation of Buchanan and Lloyd's (1997) initial direction-dependent protocol to examine muscle activation strategies about the knee was the non-weight-bearing aspect. Activities of daily living generally occur while weight-bearing therefore their results were not generalizable to functional movements. Weight-bearing exercises

are commonly used in rehabilitation programs as previous studies suggest these exercises provide an optimal opportunity for cocontraction of the lower limb compared to non-weight-bearing exercises (Ebben et al, 2009; Begalle et al., 2012). Along with a greater cocontraction during weight-bearing exercises comes an increase in tibiofemoral contact force, providing greater stability to the knee joint by limiting the displacement and rotation which protects ligaments from excessive straining (Markolf et al., 1981). Therefore, utilising an isometric weight-bearing protocol is beneficial when examining muscular activation patterns that provide static knee joint stability in multiple directions.

Based on Buchanan and Lloyd (1997), Flaxman (2011) modified the direction-dependent force matching protocol to investigate muscle activation patterns and knee joint stabilisation strategies while weight-bearing. Flaxman et al. (2012) measured mean muscle activation, based on ground reaction force orientation in twelve directions about a circular trajectory, and Smith et al. (2012) confirmed the reliability of the protocol. Three major roles for muscles in knee joint stabilisation while weight-bearing were defined: (1) *general joint stabiliser*, (2) *specific joint stabiliser*, and (3) *moment actuator* (Flaxman et al., 2012). This confirms the previous suggestion that the relationship of moment arm orientation and direction of peak muscle activation is more complex than previous thought (Buchanan & Lloyd, 1997). Results suggest muscles acting as knee joint stabilisers (Vastus Lateralis, Vastus Medialis, Biceps Femoris) increase joint compressive forces, which creates a stable mechanical linkage at the knee from which moment actuators (Semitendinosus) can initiate directed forces (Flaxman et al., 2012). This information is valuable to future investigations on the variation of activation patterns of

knee joint stabilisers in different populations. This protocol was used as the methodology of the present study.

Theoretical Framework and Hypotheses

Hypothesis 1: Sex-related differences in muscular activation patterns (Aim 1)

It has been suggested that females have different neuromuscular stabilisation strategies than males, which may be a major factor in the development and progression of OA. An increase in normalised EMG activity during static and dynamic tasks coincides with a decrease in quadriceps strength and muscle volume in older females with OA (Berger et al., 2012). Therefore, we hypothesise that (H1) healthy, older females will exhibit greater normalised EMG activity and reduced muscle specificity, resulting in a greater number of *general joint stabilisers*, compared to healthy, older males.

Hypothesis 2: Neuromuscular adaptations associated with males and females with OA (Aim 2)

Compared to age-matched controls, studies report OA participants produce greater levels of normalised EMG activity of the lower limb during dynamic tasks (Schmitt & Rudolph, 2007; Heiden et al., 2009a). With greater self-perceived joint instability, people with OA suffer from muscle strength imbalances and may use this greater EMG activity, leading to reduced muscle specificity, to compensate. Therefore we hypothesise (H2) people with OA will utilise reduced muscle specificity and greater EMG activity, in turn having more *general joint stabilisers*, compared to healthy controls, to a greater extent in females.

Hypothesis 3: Quadriceps and hamstrings muscle weakness/dysfunction (Aim 3)

Quadriceps weakness in older females with and without OA is in part a result of the inability to recruit all muscle fibres (Lewek et al., 2004) explaining their need for increased effort to produce functional movements. The results of aim 2 led to our findings that, while no knee flexor strength differences were found between healthy and OA-affected adults, females with OA utilised significantly greater levels of biceps femoris activity than healthy females suggesting increased activation may be in response to joint degeneration warranting further investigation into hamstring function. Therefore, we hypothesise that (H3i) OA participants and healthy females controls will have greater quadriceps inhibition than healthy male controls and (H3ii) females with OA will have the greatest knee flexor inhibition.

2. METHODOLOGY

Study Design

This study examined the sex differences in knee joint stabilisation strategies within and between a knee osteoarthritis group and a healthy, control group during a weight-bearing target matching protocol. It used normalised muscular activation levels of eight muscles crossing the knee joint to determine neuromuscular adaptations used to stabilise the knee joint. Ground reaction force (GRF) data of the test limb were normalised to each individual's maximum GRF in four directions (±x, representing medial/lateral loading directions; ±y, representing anterior/posterior). This design allowed the investigation of isometric knee joint stabilisation strategies in male and female older healthy adults and male and female older adults with knee osteoarthritis.

Participant Criterion and Recruitment

Four groups, males with knee osteoarthritis, females with knee osteoarthritis and healthy (control) males, and healthy females participated in this study. A post-hoc power analysis using G*Power (3.1.0) software determined a group size of 14 had >0.80 power to effectively test our hypotheses with ANOVAs. Partial eta squared for mean muscle resultant magnitude was entered into the program to calculate the effect size (0.47). Another post-hoc power analysis using G*Power (3.1.0) software determined group sizes of 18 and 17 for our analysis on male and female older, healthy adults had 0.58 power and an effect size of 0.64, as calculated by the mean and standard deviation mean muscle resultant magnitude of both groups. Participants were all over the age of 50, as prevalence of OA above this age is high, and participated in regular physical activity at least two days a week. Exclusion criteria for both groups included: a significant lower limb injury (i.e. ligament rupture); a lower limb fracture; a lower extremity motor nerve lesion; the presence of a knee joint effusion; diabetes, or any other reported physical impairment that could affect the results of the study, within six months of participation, and/or BMI $\geq$35kg/m^2. Healthy controls were excluded if their Knee Osteoarthritis and injury Outcome Score (KOOS) subscale scores classified them as having symptomatic knee OA (Lohmander et al., 2004). The healthy group was recruited from posters in the Ottawa community and the knee osteoarthritis group was recruited from the Ottawa Hospital, Ottawa community centres, and physiotherapy clinics throughout Ottawa and were diagnosed with radiographic knee osteoarthritis by a general practitioner. Affected limb(s) were recorded for all participants and OA severity was recorded for those who participated in the winter/spring of 2013-2014. All participants read and signed a consent

form prior to data collection. The University of Ottawa Research Ethics Board approved this study.

Equipment and Data Collection

KOOS and Physical Activity Levels

Each participant filled out the Knee injury and Osteoarthritis Outcomes Score (KOOS) (See: Appendix A) prior to data collection. The KOOS' rating of symptoms, pain, ADL, sports, and QoL are on a scale of 0 to 4 (Roos et al., 1998). The KOOS is a valid and reliable tool for measuring symptoms in older adults with OA (Roos & Lohmander, 2003). KOOS scores were totalled and the results between groups were examined at the end of the data collection. All participants reported the frequency, intensity, type, and time (FITT) of physical activity they participated in during an average week.

Muscle Activations

Eight bipolar single differential silver surface electrodes (SP-E04, DE 2.1, Delsys Inc., MA) 10mm in length, 1mm wide, and spaced 10mm apart were secured to each participant's test limb for data collection. Electrodes were connected to a portable input module (SP-N05, Bagnoli-8, Delsys Inc., Boston, MA) attached to a custom harness worn by the participant. The grounding electrode (Dermatrode HE-R Farmado, BV, Nuland, Netherlands) was placed on the clavicle. The system unit was amplified via a connection to the main amplifier unit (SP-B08, Bagnoli-16, Delsys Inc., Boston, MA). Surface EMG was sampled at 1000Hz, amplified by a gain of 1000, and band-pass

filtered between 20-450Hz using a 16 bit A/D conversion Board (NI PCI 6229, National Instrument Corp., Austin TX).

Force Measurement

A Bertec force platform (FP4060-08, Bertec Corporation, Columbus, OH, USA) was secured in the floor of the laboratory with a size-appropriate water-ski boot fixed to it. The platform recorded at 1000Hz and was used to measure GRF data.

Kinematics and Kinetics Measurements

A ten-camera infrared motion analysis system (Vicon MX-13, Oxford Metrics, Oxford, UK) recorded marker trajectories at 200Hz. *Nexus* software (v. 1.7, Oxford Metrics, Oxford, UK) was used to record and output three-dimensional kinematic and kinetic data of the lower limb, specifically hip, knee and ankle joint angles and moments. Joint angles were measured to verify joint position throughout the target matching protocol.

Biodex Multi-Joint System 4 Pro

Maximum voluntary isometric contraction (MVIC) data were collected using an isokinetic dynamometer (850-000, Biodex, Shirley, NY). The analog signals of torque and position were exported through the remote access port of the isokinetic dynamometer in real time at 1000Hz to an A/D conversion board (NI PCI 366229, National Instrument Corp., Austin, TX) and collected using a custom-made application (Labview 8.20, National Instruments Corp., Austin, TX).

Target Match Software

Target Match Software is a custom designed *Matlab* application (2007b, Mathworks, Natick, MA), which sets the required task parameters of the knee

stabilisation protocol and collects EMG and GRF data. The purpose of this program is to promote direction specific, isometric muscle activations during weight-bearing loading.

Protocol Setup

Participant Setup

Each participant was welcomed to the lab and asked to complete the consent form and KOOS survey. Participants were encouraged to answer as honestly and accurately as possible to provide the most reliable scores. Participants were asked what/if any medications they were taking, as well as the FITT of physical activity they participated in during an average week. Participants were fitted with a black spandex t-shirt and shorts to allow for necessary access when attaching EMG electrodes, as well as for more accurate marker placement throughout the protocol. Each participant's height (cm), weight (kg), age, sex and lower limb and pelvis anthropometrics were then recorded and entered into *Nexus* software. Each participant then completed a practice trial of maximum isometric weight-bearing loads and target match (matching a cursor to each of the twelve targets once (See: Target Matching Protocol below)). Following the practice trial of the target matching protocol, bipolar surface EMG electrodes were placed on the muscle bellies of eight muscles on each participant's test leg: rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), long head of the biceps femoris (BF), semitendinosus (ST), tensor fascia latae (TFL), lateral gastrocnemius (LG), and medial gastrocnemius (MG). Electrode placement on the muscle bellies were determined by palpation during manual resisted isometric contraction according to SENIAM (Hermens et al., 2000). Various functional exercises were used to check the EMG signal to noise ratio (Hermens et al.,

2000). To maximize muscle activity conduction, prior to electrode placement the skin surface was vigorously wiped clean with an alcohol swab and if necessary, hair was shaved with a disposable razor (DeLuca, 1997). Following maximum voluntary isometric contraction data collection (See: Maximum Voluntary Isometric Contraction below), forty-five reflective markers (14mm diameter) were placed on the upper and lower bodies of each participant according to a modified Plug-in Gait model marker set (Beaulieu et al., 2010).

Maximum Voluntary Isometric Contraction (MVIC)

Participants performed a 5-minute warm up on a stationary bike (Monarch AB, Sweden; 90 RPM with no resistance) to warm up their muscles before performing various lower limb maximum voluntary isometric contractions on their test leg. BIODEX Multi-Joint System 4 Pro was used to measure isometric strengths at the ankle, knee, and hip joints. Plantar flexion, knee extension, and knee flexion of each participant's test leg was tested in a seated position with relaxed hip, knee, and ankle joints at 30° flexion, 30° flexion, and 10° plantar flexion, respectively. Hip abduction was tested in a standing position with a neutral (0°) hip and knee. Participants were instructed to ramp up their force from 0-100% effort over a few seconds and hold their maximum for at least three seconds. EMG signals and joint torque were recorded and analyzed by custom-made software (Labview v.8.20, National Instruments Corp., Austin, TX). Verbal encouragement from the researchers was provided. The Biodex is a proven reliable tool for measuring isometric contractions (Drouin et al., 2004). The protocol places participants seated and secured in place by straps and attachments, decreasing the opportunity for a change in joint angle and contribution to torque development from

surrounding muscles.

Maximum Isometric Weight-bearing Loads

Each participant faced a screen approximately three meters away from their position that had visual feedback projected on it. Each participant's test leg, for healthy controls and those with bilateral OA: determined by the leg used to kick a soccer ball as far as possible and for unilateral OA: determined by the affected limb, was secured in a size-appropriate water-ski boot (Bio, O'Brien, Redmond, WA) that was fixed to a force platform (FP4060-08, Bertec Corporation, Columbus, OH). The test limb maintained a position of 30° hip flexion, 30° knee flexion, and 10° ankle plantar flexion with the participant's hips squared to their shoulders. The support limb was positioned posteriorly and shoulder width apart from the test foot to allow the participant to comfortably maintain specified joint angles of the test limb during the protocol. The support limb was in the participant's shoe to minimize leg length asymmetry and mediolateral pelvic tilt. Tape was placed on either side of the shoe to maintain foot placement for all trials.

Participants began the protocol by distributing equal body mass to each limb, which was expressed by a scale on the screen. Then, they exerted a maximal GRF against the force platform in each of the anterior/posterior (±y) and medial/lateral (±x) loading directions (Fig. 1), as well as internal and external rotation directions (Fig. 2A).

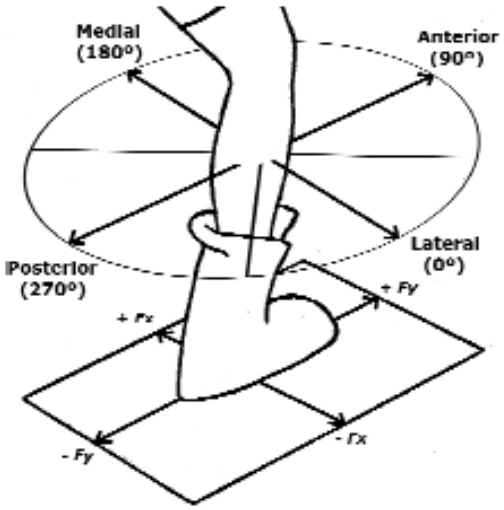

Figure 1: Example of laboratory set-up with a participant's foot in a ski boot attached to a force platform. Directions representing lateral, anterior, medial, and posterior are 0°, 90°, 180°, and 270°, respectively (Flaxman, 2011).

Target Matching Protocol

Researchers used a weight-bearing target matching protocol (Flaxman, 2011) to assess participants' voluntary muscle activation patterns while isometrically modulating GRF (Flaxman et al., 2012). These reaction forces were similar to forces experienced in daily living (McClay et al., 1994). This methodology has previously investigated muscle activation strategies in young (24±2 years) and older (59±5 years) healthy participants (Smith, 2012; Flaxman et al., 2014).

Throughout the protocol, participants' aimed to maintain hip, knee, and ankle joints in the same position held during the maximal isometric weight-bearing loads testing. A projected image of a cursor and a target were placed in front of the participant providing visual feedback of the direction and magnitude of GRF applied to the force platform. GRF controlled the cursor which moved with three degrees-of-freedom: 1) anterior/posterior loads (force along the ±y axis) move the cursor upward/downward, 2)

medial/lateral loads (force along the ±x axis) move the cursor to the left/right, and 3) inferior/superior loads (force along the ±z axis) make the cursor smaller/larger i.e. controlling the percent body mass applied to the ground (Fig. 2A). The maximum isometric weight-bearing data was used to normalise the target locations by 30% ±3.6**%** of the peak load recorded GRF in the horizontal plane. The inferior/superior (±z) load required to maintain the cursor on the target was set at 50% ±5% body mass. Internal and external rotation isometric forces were set to 100% of the peak force in the maximal testing. Each participant was required to successfully match the cursor over the target for half a second (during which forces in all directions must match the target specifications). This triggered collection of surface EMG, marker trajectories, and GRF for four seconds (three-and-a-half seconds prior to the matched target and the half-second the target is matched). Twelve targets appeared in directions spaced by 30º about a circular trajectory (Fig. 2B) and participants were required to match each cursor three times for a total of 36 trials. The targets appeared on the screen in a randomized order. Participants were prompted to relax once a target had been matched and they were given a minimum of 30 seconds to rest between trials. They were encouraged by the researchers to go at their own pace to prevent fatigue.

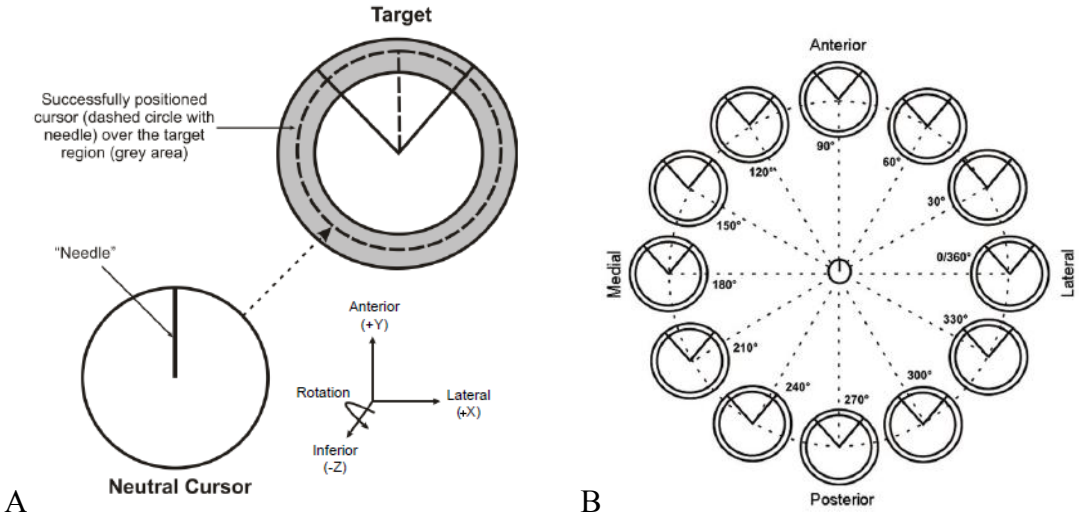

Figure 2: (A) Example of a successful match: participants maintain GRF at 30% of maximum isometric loads (based on target direction) while maintaining 50% BM on the test limb. (B) Direction of all twelve targets evenly spaced about a circular trajectory (Flaxman, 2011).

Skipped Steps

The demands of the target match task were difficult to meet for some participants. A custom-made *Matlab* application determined if skipped targets had half a second of data where all forces were within an acceptable range (30%±10% maximum GRF- Fx, Fy, and 50%±5%- Fz). This range was determined by calculating the greatest percentage of error that occurred within successful trials. Due to the reduction in neuromuscular control in older populations, participant data was included if data of at least one trial of each target was within an acceptable range.

Walking and Squat Trials

Following the target matching protocol, the researcher removed the ski boot from the force platform and moved the screen and projector to allow space for five walking trials and three bi-limb squats. Each participant practiced the walking trial prior to collection until they walked comfortably in the space and to mark the starting point that accurately placed their test foot on the force platform after approximately three walking

strides. Five successful walking trials at a self-selected pace and three bi-limb squats with a pause at the end of each squat were completed. The range for the squat was not standardized due the variability in range of motion of the participant population. Marker trajectory, GRF, and EMG for successful walking and squat trials were recorded using *Nexus* software (v. 1.7, Oxford Metrics, Oxford, UK). This data was not used in the analysis of this study however may be processed and analyzed in future research.

Participation Requirements

Participants visited the Human Movement Biomechanics Laboratory located at 200 Lees Ave., room E020 for the data collection on one day for approximately four hours. As approved by the ethics committee, the parking fee or public transportation fare was reimbursed after proof of payment was presented, and participants were thanked for contributing to the project. They were also informed they would receive the results of the study after its completion. There were no safety/wellbeing concerns in the protocol, however maximal muscle contractions were measured and the target matching protocol may have caused temporary fatigue and discomfort. Participants were encouraged to inform the researchers if they were feeling discomfort of any kind throughout the session. Participant confidentiality was secured, as all data was recorded under a subject code, for example FOA001.

Data Analysis

Maximum Voluntary Isometric Contraction

A custom-made *Labview* application loaded EMG data from MVIC, full wave

rectified and filtered it using a 4th order Butterworth dual low-pass filter with a cut-off frequency of 6Hz. An Excel spreadsheet determined the maximum muscle activity for each of the eight muscles during the four movements tested. Fifty data points (50ms) before and after the maximum EMG value were averaged and this value was used to normalise the EMG data of the target matching protocol. The same custom-made *Labview* application was used to load and filter torque data for each of the four movements using a 4th order Butterworth dual low-pass filter with a cut-off frequency of 6Hz. A custom-made *Matlab* application (2010b, Mathworks, Natick, MA) determined maximum torque produced (averaged fifty data points (50ms) before and after the maximum torque value) and the cell index of peak torque for each of the four movements. The cell indices were used to call the corresponding filtered muscle activation of each of the eight muscles to determine muscle activity at the time of peak torque production. Fifty data points (50ms) before and after the indexed cells were averaged and normalised to the maximum EMG of each muscle.

Target Matching

The Target Matching Software *Matlab* application was used to digitally synchronize EMG, GRF, and kinematic data corresponding to each successful target match. Kinematics were filtered with a 4th order zero-lag Butterworth filter (20Hz) using *Nexus* software. This software calculated hip, knee, and ankle joint angles and moments in accordance with the modified Plug-in-Gait model (Beaulieu et al., 2010). Processed kinetics and kinematics were averaged across successful trials for each target using a custom-made *Matlab* application.

EMG data was bias corrected, full wave rectified and filtered (4th order

Butterworth dual low-pass (6Hz)) in the custom-made *Matlab* application mentioned in the MVIC section. The test limb's EMG signals were normalised to MVIC then time averaged and ensemble averaged across successful trials, corresponding to an EMG vector (EMG_i). EMG_i were plotted in polar coordinates (x, y) to visually represent muscle activation patterns (Dewald et al., 1995).

The "mean magnitude of muscle activity" was computed for all eight muscles by averaging all the normalised EMG_i at every target location:

$$X_{EMG} = \frac{\sum EMG_i}{n}$$

GRF (Fx, Fy, Fz) were filtered (4^{th} order Butterworth dual low-pass filter with a cut-off frequency 20Hz) and averaged across successful trials for each target using a custom-made *Matlab* application.

Muscle Activation Patterns

To quantitatively describe the muscle activation patterns, asymmetry about the polar plot origin was tested using methods by Curray (1956):

$$p = e^{L^2 n} 10^{-4}$$

where p is the probability of observing non-random asymmetry, e is the base of the natural logarithm, L is the mean vector magnitude, and n is the number of observations. The asymmetry was considered significant if $p<0.05$ indicating muscle activation was greater in one GRF direction relative to another.

The "mean direction of muscle activity" (ϕ) was determined for muscles with asymmetrical activation:

$$\phi = \tan^{-1}\left(\frac{\sum y_i}{\sum x_i}\right)$$

where x_i and y_i are the Cartesian coordinates.

Specificity Index

The variance of muscle activation about the ϕ was described as the "specificity index" (SI), which was derived from the ratio of the muscle's actual resultant vector to its absolute resultant vector (Dewald et al., 1995; Williams et al., 2003):

$$SI = \frac{\left[\left(\sum x_i / n\right)^2 + \left(\sum y_i / n\right)^2\right]^{-1/2}}{\left[\left(\sum |x_i| / n^2\right) + \left(\sum |y_i| / n\right)^2\right]^{-1/2}}$$

The SI ranged from 0.0:1.0. 0.0 indicated a muscle was equally active in all target directions (completely non-specific stabilisation strategy), and 1.0 indicated a muscle was only active at one target (completely specific stabilisation strategy).

Torque Production and Corresponding Muscle Activations

Subject-specific knee extension and flexion strength and EMG data collected during MVIC data were combined with a modeling framework to determine optimal muscle strength scale parameters. OpenSim Gait-2354 model (Thelen et al., 2013) was used to extract moment arms of the muscles with joint angles set at 30° hip and knee flexion, and 10° ankle plantar flexion. Using optimization, the maximum isometric force of the muscle (Delp et al., 1990) was tuned to minimise the error between the simulation and the experimental torques with lower and upper scale bounds set to 0.2 and 6.0, respectively.

The parameter $F_0^{\max}$ of each agonist muscle was scaled by the level of normalised EMG in order to calculate each muscle's force at peak torque. That scaled muscle force

was multiplied by the muscle's moment arm to calculate the maximum torque capacity corresponding to that muscle. The *Ideal* peak torque represented the knee extensor/knee flexor muscles' full capacity as all agonist muscle forces were set at 100% with antagonist muscles producing no opposing force. A voluntary activation ratio (a_i):

$$a_i = T^b / T^I$$

represented quadriceps and knee flexor inhibition, where T^b is the *Experimental* (Biodex) peak torque and T^I is the *Ideal* peak torque (lower value represents greater inhibition).

Statistical Analysis

Aim 1: A polar plot analysis of the EMG_i polar coordinates determined the X_{EMG} and ϕ for each muscle. Sex differences in age, BMI, KOOS, absolute and normalised peak torque, X_{EMG}, and SI were determined using independent t-tests. A mixed model analysis of variance (ANOVA) was used for each muscle to determine between-group differences in mean muscle magnitude by direction. Multivariate analyses of variance (MANOVAs) were used to determine sex differences in absolute GRF (axes- *x, y*), joint angles, and joint moments (axes- *x, y, z*) at each target direction. Sex differences in normalised GRF (axes- *x, y*) were also analysed with MANOVAs for targets in the lateral, anterior, medial, and posterior directions. An adjusted alpha level was used for the MANOVAs based on the number of plane-dependent variables. In the case of significance, a post-hoc analysis was run using independent t-tests to determine if a difference occurred in specific loading directions. Between-group differences in ϕ were determined for each muscle using Watson-Williams test for circular statistics in PAleontological STatistics (PAST) (Hammer et al., 2001). Intra-class correlation

coefficients ($ICC_{(2, k)}$) (Shrout & Fleiss, 1979) were used to describe the variance in muscle activation between targets across all participants within each group. ICCs and standard error of measurement (SEM) (Portney & Watkins, 2000) determined the reliability of each muscle's activation pattern between-subjects in each group.

Aim 2: Three group comparisons were analysed: Male OA-Female OA, Male OA-Male OC, and Female OA-Female OC. For each of the eight muscles tested, one-way ANOVA with three planned comparisons were used to identify the variation between groups' age, BMI, KOOS total score, absolute and normalised peak torque, X_{EMG}, and SI. Mixed model ANOVAs were used to determine between-group differences in KOOS subscale scores. Analyses for between-group differences in ϕ, absolute GRF, normalised GRF, joint angles and moments, and mean muscle magnitude by direction were completed for each pair using the same tests as described in *Aim 1* and included an adjusted alpha level of 0.025 to account for both male and female OA being used in the analysis of a second comparison. In the case of significance, a post-hoc analysis was run using an ANOVA with planned comparisons, or an independent t-test to determine if a difference occurred in a specific loading direction. Pearson's correlation coefficient was used to examine the extent of the linear relationship between KOOS scores and age of OA-affected adults. Between-subject reliability measures (ICC, SEM) were also the same as described in *Aim 1*.

Aim 3: One-way ANOVA tests were used to determine between-group differences in KOOS subscale and total scores, absolute and normalised peak knee extension and flexion torque (Nm), and knee extensor and flexor torque deficiencies. A MANOVA was used to determine between-group differences in quadriceps muscle contribution ratios to

peak knee extension, as well as in BF, ST, LG, and MG contribution ratios to peak knee flexion torque. An adjusted alpha level of 0.017 was used for quadriceps contribution as three quadriceps muscles were tested, and an adjusted alpha level of 0.0125 was used for knee flexor contributions, as there were four knee flexors tested. In cases of significance, a post-hoc test was run to locate the between-group difference.

The statistical analysis software *SPSS* (v.21.0, IBM, Chicago, IL) was used with an alpha level of 0.05 for all tests unless otherwise stated.

ARTICLE 1: SEX DIFFERENCES IN STABILISATION STRATEGIES OF OLDER ADULTS DURING WEIGHT-BEARING DIRECTION-DEPENTDENT LOADING

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Abstract

Muscles have individual roles in providing stability to the knee joint that are more complex than previously thought. Sexes appear to adopt different roles as a result of neuromuscular adaptions, such as increased muscle activations. However, the fundamental roles of individual muscle contributions to joint stability and the effect neuromuscular adaptations have on joint loading have not been fully explored in healthy older adults. This in part is due to the biomechanical complexities during dynamic tasks. The aims of this study were: i) to investigate sex differences in knee joint stabilisation strategies and to identify each muscle's role in joint stabilisation in older adults (n=36) during highly-controlled, direction-dependent loading; and ii) to investigate sex differences in peak torque production during lower limb maximum voluntary isometric contractions (MVICs). A weight-bearing target match protocol with twelve targets, representing various combinations of ground reaction forces normalised to 30% maximum, was used to identify joint stabilisation strategies. Mean muscle magnitude was plotted in polar coordinates based on target direction to display muscle activation patterns. Mean resultant magnitude (X_{EMG}) of each muscle was calculated to determine sex differences in mean muscle activation levels. A specificity index (SI), mean direction of magnitude (ϕ), and a test of asymmetry, were used to determine fundamental roles of stabilisation for eight muscles of the lower limb. An isokinetic dynamometer measured the peak torque of knee extension, knee flexion, ankle plantar flexion, and hip abduction during MVICs. Rectus femoris (RF), vastus medialis, vastus lateralis, and tensor fascia latae all had symmetrical activation patterns and were classified as general joint stabilisers (relatively low SI, non-interpretable ϕ). Females demonstrated greater RF

X_{EMG} (p=0.067) and lower BF X_{EMG} than males (p=0.084). Statistical analysis showed that stabilisation roles of all muscles except lateral gastrocnemius (LG) had no significant difference between sexes. Biceps femoris (BF) and medial gastrocnemius acted as specific joint stabilisers due to asymmetrical activation patterns, relatively high SI, and in males, ϕ=199°, 157°, and in females ϕ=184°, 144°, respectively. Semitendinosus' role was moment actuator, represented by asymmetrical activation pattern, relatively high SI, and ϕ=248° and 257° in males and females, respectively. Females had a significantly lower SI of LG along with a symmetrical orientation compared to males' asymmetrical orientation and high SI; therefore, their role differed between sexes: a general stabiliser in females and a specific stabiliser in males. Our moderate-high reliability in activations between subjects in six of eight muscles (ICC= 0.529-0.958), along with low standard error of measurement between subjects (0.037-0.137) in all muscles, suggests our results are representative of a non-random neuromuscular control strategy. Females produced significantly less absolute peak torque of all four lower limb movements ($p<0.05$) while no significance was found when peak torque was normalised to body mass ($p>0.05$).

In conclusion, we identified increased RF activation, reduced BF activation, and reduced muscle specificity in healthy, older females compared to males and suggest these are compensatory mechanisms for reduced muscle strength. Our results indicate that improving RF, BF, and LG function could be targets for prophylactic intervention to improve muscle balance and increase knee stability under load. Future investigation into joint loading resulting from these altered strategies is warranted to advance understanding of females' increased risk of OA development.

1. Introduction

Knee joint instability is commonly reported in older adults and people with knee osteoarthritis (OA). The dominant active contributor to providing joint stability is muscle; however, reduced neuromuscular control and age-associated adaptations in muscle activation limit older adults' reliance on musculature for joint stabilisation (DeVita & Hortobagyi, 2000b). Previous studies investigated age-associated adaptations during isometric and isokinetic contractions and reported reduced muscular function (Klitgaard et al., 1990) and increased cocontraction (Hortobagyi et al., 2005), and increased normalised muscle activation (Hortobagyi et al., 2003; Madhavan et al., 2009) in healthy, older adults compared to healthy, younger adults during dynamic tasks. This increased activation has, in part, been attributed to the natural muscle atrophy that occurs with aging (Madhavan et al., 2009). It has been postulated that increased activation results in higher joint stiffness, thus reducing joint range of motion and the level of neuromuscular control required to perform a task (DeVita & Hortobagyi, 2000b). Such adaptations may provide a safer movement strategy for older adults. Negatively, changes in muscle activation strategies may alter joint loading, making older adults more susceptible to OA (Lewek et al., 2005).

Sex differences, such as less muscle mass (Slemenda et al., 1998), muscle strength (Hortobagyi et al., 1995), and greater joint laxity in females, result in a less stable joint (Huston & Wojtys, 1996), increasing risk for harmful joint loading. Quadriceps-dominance is a strategy utilised by females to maintain joint stability during activities of daily living (Youdas et al., 2007) and may be a compensatory strategy for

reduced quadriceps strength commonly reported in older females (Segal et al., 2010; Slemenda et al., 1998). Unfortunately, this strategy may alter joint loading as females with quadriceps weakness are at an elevated risk of whole knee and tibiofemoral joint space narrowing (Segal et al., 2010). Altered neuromuscular strategies and quadriceps-hamstrings muscle imbalance in females (Bencke & Zebis, 2011) reduce joint stability and has been reported in male and female anterior cruciate ligament (ACL) deficient non-copers (Rudolph et al., 2001). Rudolph et al. (2001) suggest the altered knee stabilisation strategy may increase risk of future joint degeneration. ACL and meniscus injuries are also risk factors for radiographic OA, pain, and functional limitations in females (Lohmander et al, 2004). Compensatory adaptations to stabilise the joint following ACL and meniscus injuries include reduced knee flexion and reduced quadriceps strength (Rudolph et al., 2001), mechanisms also seen in older adults with OA (Palmieri-Smith et al., 2010; Schmitt & Rudolph, 2007). This suggests these compensatory patterns have a negative impact on joint structures.

Muscle activation strategies to stabilise the knee joint have been investigated using a novel, weight-bearing ground reaction force control test and results suggest young, healthy females utilise different activation strategies than males to achieve a similar loading objective (Flaxman et al., 2014). This novel protocol is beneficial as it reduces the biomechanical complexities of investigation into muscle activation patterns that are present during dynamic tasks and allows for the identification of muscle roles as they contribute to knee joint stability. The fundamental roles have been identified as: *general joint stabilisers, specific joint stabilisers, and moment actuators* (Flaxman et al., 2012). Females demonstrated greater normalised muscle activation in rectus femoris,

lateral gastrocnemius, and tensor fascia latae, which resulted in roles as general joint stabilisers- displaying symmetrical activation patterns. In males, these muscles activated more specifically in one direction and were classified as specific joint stabilisers represented by asymmetrical activation patterns directed away from their moment arm orientation. Previous studies have reported sex differences such as, reduced specificity of lower limb muscles during a seated target matching protocol (Krishnan et al., 2008) in young, healthy females. The roles of individual muscles as they relate to knee stabilisation strategies in older males and females have yet to be reported. This information could provide a basis for prophylactic intervention by creating training routines focusing on those muscles that have the highest potential to increase knee stability under load. Rehabilitation programs focused on the prevention of OA could thus be enhanced if sex differences in neuromuscular strategies affecting joint loading can be determined.

As such, the two aims of this study were: i) to investigate sex differences in stabilisation strategies and to identify roles of individual muscles as they relate to joint stability in older adults during a weight-bearing, direction-dependent loading task; and ii) to investigate sex differences in peak torque production during lower limb maximum voluntary isometric contractions (MVICs). Based on previous literature mentioned above, we hypothesised that i) older females will utilise greater normalised EMG, specifically of the quadriceps, and have less muscle specificity, resulting in a greater number of general joint stabilisers than similarly aged males; and ii) females would produce less absolute peak torque for all lower limb MVIC movements.

2. Methods

2.1 Participants

Forty-nine healthy, older adults were recruited from posters and word of mouth in the Ottawa area (22 males, 27 females). Inclusion criteria were being over the age of 50 and physically active at least two days a week. Exclusion criteria were significant lower limb injury six months prior to participation, diabetes, BMI $\geq$35kg/m^2, neurological or physical impairment that could affect lower limb muscle function, or Knee Osteoarthritis and injury Outcome Score (KOOS) subscale scores less than or equal to Lohmander et al. (2004) cut-offs for symptomatic knee osteoarthritis. The University of Ottawa Research Ethics Board approved this study. All participants read and signed an informed consent form prior to participation. Three males (aged 64±12, BMI 28.0±5.2kg/m^2; KOOS score 97.9±2.3) and ten females (aged 64±6 years, BMI 24.0±2.0kg/m^2; KOOS score 93.2±9.0) of those recruited were unable to complete the protocol (successfully match every target at least once). Therefore, 19 males and 17 females completed the protocol and were included in the data analysis.

2.2 Experimental Protocol

2.2.1 Knee health ratings and physical activity levels

All participants completed the KOOS survey (Roos et al., 1998), which evaluates knee-related symptoms, pain, function/daily living, function/sports and recreation, and quality of life. Ratings were on a 5-point Likert scale, and scores were converted to a total score between 0 and 100 (worst and best). Participants also reported the frequency,

intensity, type, and time per week of physical activity they participated in during an average week.

2.2.2 Maximum voluntary isometric contractions

Participants warmed up for 5 minutes on a stationary bicycle (Monarch AB, Sweden; 90 RPM, no resistance) prior to performing maximum voluntary isometric contractions (MVICs) on a dynamometer (850-000, Biodex Medical Systems, Shirley, NY). Knee extension, knee flexion, and ankle plantar flexion were collected in a seated position with hip, knee, and ankle joints at 30° flexion, 30° flexion, and 10° plantar flexion, respectively. Hip abduction was collected standing with a neutral (0°) hip and knee. Participants were asked to ramp up force and hold their maximum for approximately three seconds. Three trials of each movement were collected. The analog signals of torque and position were exported through the remote access port of the isokinetic dynamometer in real time at 1000Hz to an A/D conversion board (NI PCI 366229, National Instrument Corp., Austin, TX) and collected along with EMG using a custom-made *Labview* application (v.8.20, National Instruments Corp., Austin, TX).

2.2.3 Direction-dependent loading

A weight-bearing target matching protocol was used in this study (Flaxman et al., 2012, Smith et al., 2012, Flaxman et al., 2014). Participants' test foot (defined as the leg they would use to kick a soccer ball as far as possible) was secured in a size-appropriate water-ski boot fixed to a force platform (FP4060-08, Bertec Corp., Columbus, OH). Participants stood in a staggered stance with the test foot in front, feet hip-width apart, and toes pointed forward (Fig. 3). Participants wore a running shoe on the support foot to minimize leg length asymmetry and medio-lateral pelvic tilt. Tape was place around the

support foot to maintain position between trials. Hip, knee, and ankle joint angles of the test limb were 30° flexion, 30° flexion, and 10° plantar flexion, respectively.

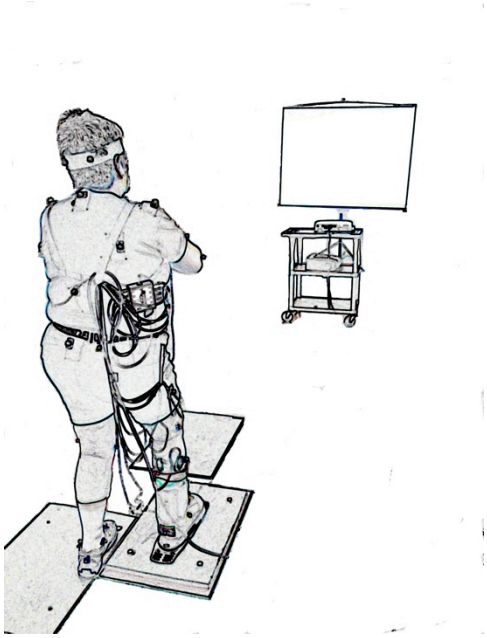

Figure 3: Laboratory setup of participant standing on force platform in front of a screen.

Participants began by distributing even body mass (BM) to each limb while receiving visual feedback on a screen approximately three meters in front of them. Participants maintained even BM and the above-mentioned joint angles while exerting maximal ground reaction forces (GRF) against the force platform in anterior-posterior (±Fy), medial-lateral (±Fx) loading directions, and internal and external rotation. Participants controlled a circular cursor on the screen by modifying their GRF. The cursor moved upwards/downwards and left/right representing anterior/posterior and medial/lateral forces. The size of the cursor increased as the proportion of BM on the test limb increased, and decreased as the BM proportion decreased (±Fz). Twelve targets evenly spaced about a circular trajectory appeared on the screen in a randomized order. The targets at 0°, 90°, 180°, and 270° represented lateral, anterior, medial, and posterior directions, respectively. A successful trial was defined as matching the cursor to the

target for a half-second (Fig. 4). This required 30% ±3.6% maximal Fx and Fy for targets while maintaining 50% ±5% Fz and internal/external rotation forces limited to the maximum trial levels. A successful trial triggered simultaneous collection of EMG, GRF, and kinematics for four seconds (three-and-a-half seconds prior to the successful match, and the half-second the target was matched). Each participant completed three trials of each target. Participants were prompted to relax after each successful trial and were encouraged to rest between trials to prevent fatigue. A practice set of all twelve targets was completed on the same day prior to testing.

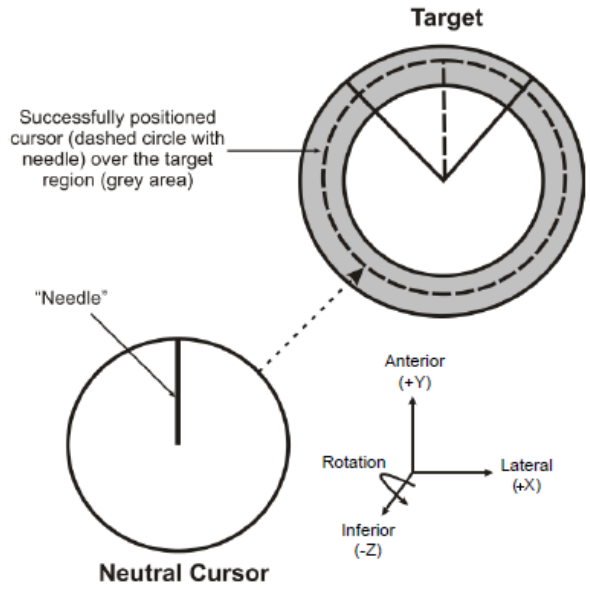

Figure 4: Example of a target normalised to participant's maximum GRF required for a successful match. (Flaxman, 2011)

2.2.4 Kinematics and Kinetics

Forty-five reflective markers (14mm diameter) were placed on the upper and lower bodies of each participant according to a modified Plug-in Gait model marker set (Beaulieu et al., 2010). Marker trajectories were captured by a ten-camera infrared motion analysis system (Vicon MX-13, Oxford Metrics, Oxford, UK) and recorded at 200Hz. GRF were captured using a force platform (FP4060-08, Bertec Corp., Columbus,

OH) and were recorded in *Nexus* (v.1.7, Oxford Metrics, Oxford, UK) at 1000Hz. Kinematics and GRF were filtered with a 4th order zero-lag Butterworth filter (20Hz) using *Nexus* software (v.1.7, Oxford Metrics, Oxford, UK). This software calculated hip, knee, and ankle joint angles and used inverse dynamics to calculate moments in accordance with the modified Plug-in Gait model (Beaulieu et al., 2010). Processed joint angles, moments, and GRF were time averaged for the successful half-second, and then ensemble averaged across successful trials for each target using custom-made *Matlab* applications (2007b, Mathworks, Natick, MA).

2.2.5 Electromyography

Bipolar surface electrodes (SP-E04, DE 2.1, Delsys Inc., MA) 10mm in length, 1mm wide, and spaced 10mm apart, were placed on the muscle bellies of rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), semitendinosus (ST), lateral gastrocnemius (LG), medial gastrocnemius (MG), and tensor fascia latae (TFL) according to SENIAM guidelines (Hermens et al., 2000). A ground electrode was placed on the right clavicle (Dermatrode HE-R Farmado, BV, Nuland, Netherlands). Skin was cleaned with an alcohol swab and shaved (if necessary) prior to electrode placement to reduce noise (DeLuca, 1997). EMG was sampled at 1000Hz, amplified by a gain of 1000, band-pass filtered at 20-450Hz using a 16-bit A/D conversion board (NI PCI 6229, National Instruments Corp., Austin, TX), and recorded by a custom-made *Matlab* application (2007b, Mathworks, Natick, MA). MVIC EMG data was full wave rectified, bias removed, and filtered with a 4th order Butterworth dual low-pass filter (6Hz) and MVIC torque data was bias removed and filtered with a 4th order Butterworth dual low-

pass filter (6Hz) in a custom-made *Labview* application (v.8.20, National Instruments Corp., Austin, TX). Each muscle's MVIC value and each movement's peak torque values were calculated by averaging fifty ms before and after its maximum value. Target match EMG was full wave rectified, bias removed, filtered with a 4th order Butterworth dual low-pass filter (6Hz), and normalised to MVIC in a custom-made *Matlab* application (2007b, Mathworks, Natick, MA). The half-second of matched target data was time-averaged and then ensemble-averaged across repetitions. Average EMG corresponded to an EMG vector (EMG_i), its respective orientation and magnitude representing loading direction and normalised muscle activation. EMG_i were plotted with polar coordinates to display muscle activation patterns. The mean resultant magnitude of muscle activity (X_{EMG}) was computed for each of the eight muscles by averaging all the normalised EMG_i at every target location:

$$X_{EMG} = \frac{\sum EMG_i}{n}$$

To identify the functional roles of the muscles we define them as a general joint stabiliser, specific joint stabiliser, or moment actuator as follows. General joint stabiliser has a symmetrical activation pattern determined by a non-significant test of asymmetry, relatively low specificity index (SI), and a non-interpretable mean direction of activity (ϕ). A specific joint stabiliser has an asymmetrical activation pattern opposite its reported moment arm orientation (MAO) determined by a significant test of asymmetry and supported by a relatively high SI and its ϕ. A moment actuator has an asymmetrical activation pattern in the direction of its MAO determined by a significant test of asymmetry, and a relatively high SI and its ϕ. Curray's method (1956):

$$p = e^{L^2 n} 10^{-4}$$

tested asymmetry about the polar plot. *p* is the probability of observing non-random asymmetry, *e* is the base of the natural logarithm, *L* is the mean vector magnitude, and *n* is the number of observations. The asymmetry is considered significant if $p<0.05$ indicating muscle activation is greater in one GRF direction relative to another. If asymmetry was observed, the mean direction of muscle activity (ϕ) was determined:

$$\phi = \tan^{-1}\left(\frac{\sum y_i}{\sum x_i}\right)$$

where x_i and y_i are the Cartesian coordinates.

The degree of specificity about the ϕ for each muscle's activation pattern was quantified as the "specificity index" (SI), which was derived from the ratio of the muscle's actual resultant vector to its absolute resultant vector (Dewald et al., 1995; Williams et al., 2003):

$$SI = \frac{\left[\left(\sum x_i / n\right)^2 + \left(\sum y_i / n\right)^2\right]^{-1/2}}{\left[\left(\sum |x_i| / n^2\right) + \left(\sum |y_i| / n\right)^2\right]^{-1/2}}$$

SI ranged from 0.0:1.0, 0.0 representing a muscle that was completely non-specific (equally active in all target directions) and 1.0 a muscle that was completely specific (only active in one target direction).

2.3 Statistical Analysis

Sex differences in age, BMI, KOOS, absolute and normalised peak torque for knee extension, knee flexion, hip abduction, and ankle plantar flexion, X_{EMG}, and SI were determined using independent t-tests in SPSS (v.21.0, IBM, Chicago, IL). Multivariate analyses of variance (MANOVA) were used to determine sex-related differences at each

target direction for each of the following variables: absolute GRF, joint angles, and joint moments. MANOVAs were used to evaluate between group differences in normalised GRF for angles 0°, 90°, 180°, 270°. An adjusted alpha level of 0.025 was used for GRF tests to account for *x*- and *y*-axes and an adjusted alpha level of 0.017 was used for joint angles and moments as three plane-dependent variables were extracted for each joint (*x, y, z*). Mixed model analysis of variance (ANOVA) (2x12) was used for each muscle to determine group (2: male, female) mean differences in mean muscle magnitude by direction (12: 0°, 30°, 60°, 90°, 120°, 150°, 180°, 210°, 240°, 270°, 300°, 330°). A trend was established when $p \leq 0.10$. In the case of a trend or significance, post hoc evaluations were conducted with independent t-tests (alpha=0.05) to identify if a trend or difference occurred in specific loading directions. Watson-Williams tests were used to determine group mean differences in mean direction of muscle activity for each muscle in PAleontological STatistics (PAST) (Hammer et al., 2001). Intra-class correlation coefficients ($ICC_{(2, k)}$) (Portney & Watkins, 2000; Shrout & Fleiss, 1979) and standard error of measurement (SEM) (Portney & Watkins, 2000) were used to evaluate between-subject reliability of activation profiles in each group. An alpha level of 0.05 was considered significant for all other analyses.

3. Results

Successful trial and skipped steps: Not all participants were able to successfully match each target within our required range for half a second three times. As our protocol has proven between-trial reliability (Smith et al., 2012), we included two males and one female participant that had at least one successful trial for each target within our required

GRF range. A custom-made *Matlab* application (2010b, Mathworks, Natick, MA) was developed to determine if skipped steps, those not within the required GRF range, were within an acceptable range of 30%±10% Fx and Fy, and 50%±5% BM. One male participant had two trials within this range leading to two trials of each target to be included in the analyses.

Subject characteristics: Males' (19) and females' (17) mean±standard deviation ages (64±8, 61±5) and KOOS scores (96.1±4.3, 95.2±5.4) were not significantly different ($p>0.05$). BMI was similar, (26.0±4.1kg/m^2, 23.0±2.6kg/m^2), yet significantly different ($p=0.014$).

Absolute peak torque was significantly lower in older females for all four movements ($p<0.02$) (Fig. 5), while peak torque normalised to body mass (Nm/kg) was not significantly different between sexes ($p>0.05$).

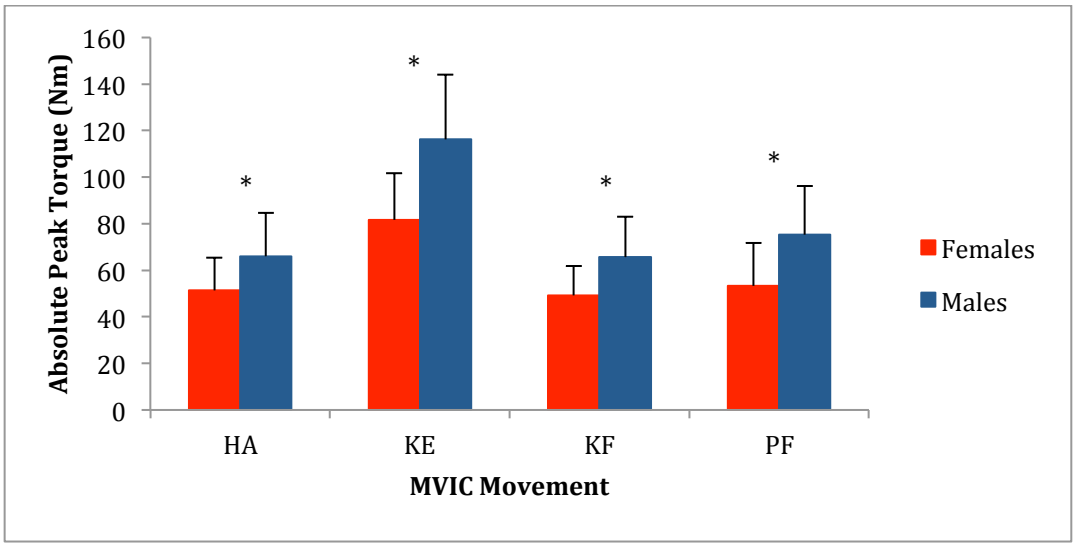

Figure 5: Mean absolute peak torque (Nm) for MVIC of hip abduction (HA), knee extension (KE), knee flexion (KF), and ankle plantar flexion (PF) in female and male older adults. Error bars represent standard deviation. Asterisks (*) represent significant differences between groups ($p<0.05$).

Kinetics and kinematics: The multivariate analysis determined there were no significant main effect of group in mean ± standard deviation normalised GRF (N/kg)

(p=0.892, 0.099, 0.231) between males (0.54±0.10, 0.53±0.12, 0.28±0.12) and females (0.55±0.12, 0.44±0.12, 0.21±0.11), in the lateral, anterior, and medial loading directions, respectively. Fy in the posterior direction was significantly different between-groups with males producing greater normalised GRF mean ± standard deviation (males: 0.38±0.09; females: 0.31±0.09) (p=0.015). Males produced significantly greater absolute GRF (N) than females in all target directions (p<0.025).

Hip flexion, knee flexion, and ankle plantar flexion mean ± standard deviation (across all targets) joint sagittal-plane angles were 23.2°±8.0, 17.6°±5.4, 4.6°±5.9 for males, and 24.8±10.0, 20.0±7.1, 7.8±5.5 for females (p=0.08, <0.001, <0.001), respectively. A covariate analysis determined the significant differences in knee sagittal-plane angle (male: 18.8°; female: 24.3°) at direction 120° had a significant effect on the magnitude of VL (p=0.031), and ankle sagittal-plane angle (male: 3.6°; female: 7.5°) at direction 180° had a significant effect on the magnitude of LG (p=0.029), however, accounting for these influences, between-group differences in normalised muscle magnitude at those directions remained non-significant (p>0.05). Hip and knee joint extension and adduction moments, and ankle joint adduction and external rotation moments were significantly different between sexes (p<0.001). Post-hoc analysis determined males produced significantly greater hip extension and adduction moments, knee adduction moments, (Fig. 6) and ankle abduction moments, and significantly less ankle external rotation moments in various directions (p<0.05). Both groups used large hip extension moments to match targets in the posterior direction (0.296-0.583Nm/kg), and large hip adduction moments to match targets in the medial direction (0.271-0.529Nm/kg) (Fig. 6).

EMG analysis: Group mean EMG polar plots displaying each muscle's activation pattern are presented in Figure 7. Females used greater RF X_{EMG} ($p=0.067$) and lower X_{EMG} of BF ($p=0.084$) compared to males (Fig. 8A). Specifically, females used greater mean magnitude of RF in directions 180°-0° ($p<0.05$) and less mean magnitude of BF in directions 150°, 210°, 240° ($p<0.05$) (Fig. 7). RF's test of asymmetry was approaching significance in males ($p=0.0568$) contrary to females ($p=0.710$). Males and females had similar asymmetrical activation patterns in BF, ST, and MG oriented in the medial (ϕ =199°, 184°), posterior (ϕ =248°, 257°), and anterior-medial (ϕ =157°, 144°) directions, respectively ($p>0.05$) (Fig. 8B). This was supported with relatively high SI values that were not significantly different between males and females, respectively ($p=0.074$, 0.356, 0.594), BF (0.306±0.148, 0.219±0.130), ST (0.330±0.139, 0.289±0.120), and MG (0.327±0.165, 0.298±0.161) (Fig. 8C). SI of RF and LG were significantly greater in males than females ($p<0.05$), and SI of BF had a trend of greater SI in males ($p=0.074$) (Fig. 7B). Along with a high SI, males displayed an asymmetrical activation pattern of LG opposing its MAO (ϕ=181)° as opposed to females that displayed a symmetrical activation pattern.

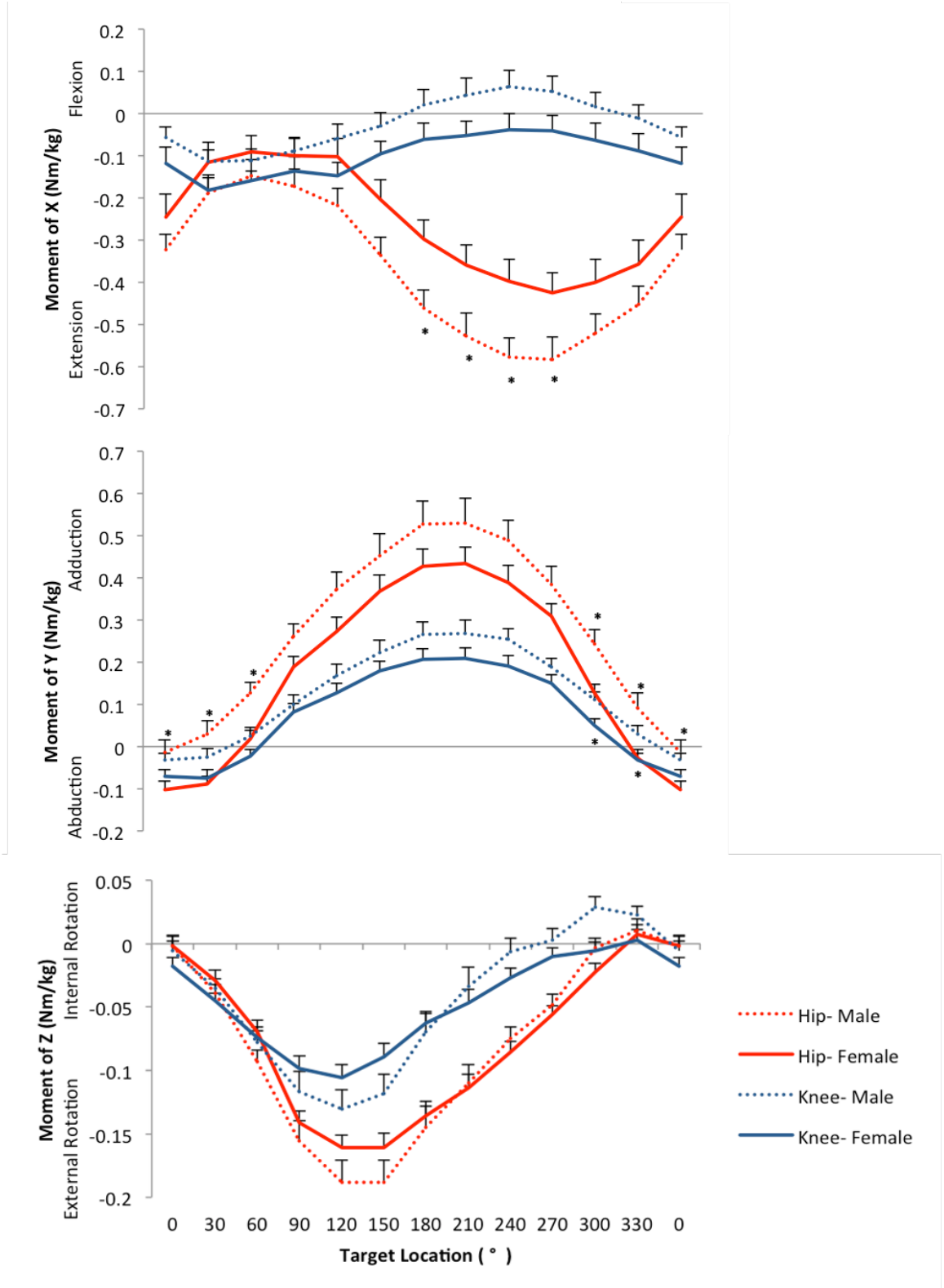

Figure 6: Group mean and standard errors of hip and knee joint moments of the (A) x-, (B) y-, (C) z-axes at each of the twelve target locations, expressed in Nm normalised to BM (Nm/kg). Asterisks (*) represent significant differences between sexes ($p<0.05$).

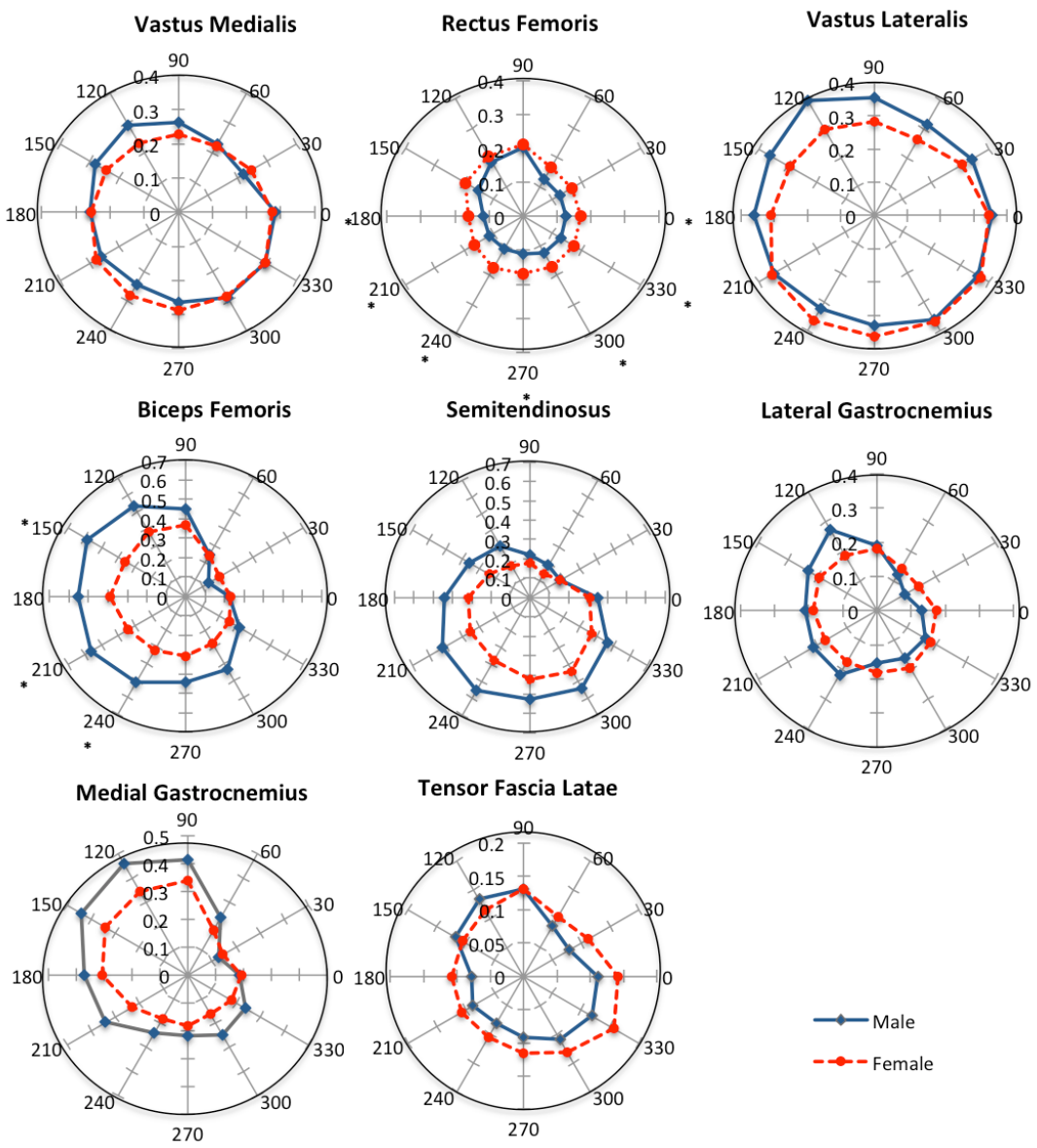

Figure 7: EMG polar plots of mean activation patterns in male and female older adults. Outer numbers represent target location angle (°). Inner numbers along each radius represent normalised EMG magnitude. In order to best illustrate sex differences, RF, VL, VM, and LG polar plots are scaled from 0 to 0.40 (40%MVIC), ST and BF are scaled from 0-0.70 (70%MVIC), MG is scaled from 0-0.50 (50%MVIC) and TFL is scaled from 0-0.20 (20%MVIC). 0°, 90°, 180°, and 270° represent lateral, anterior, medial, and posterior loading directions.

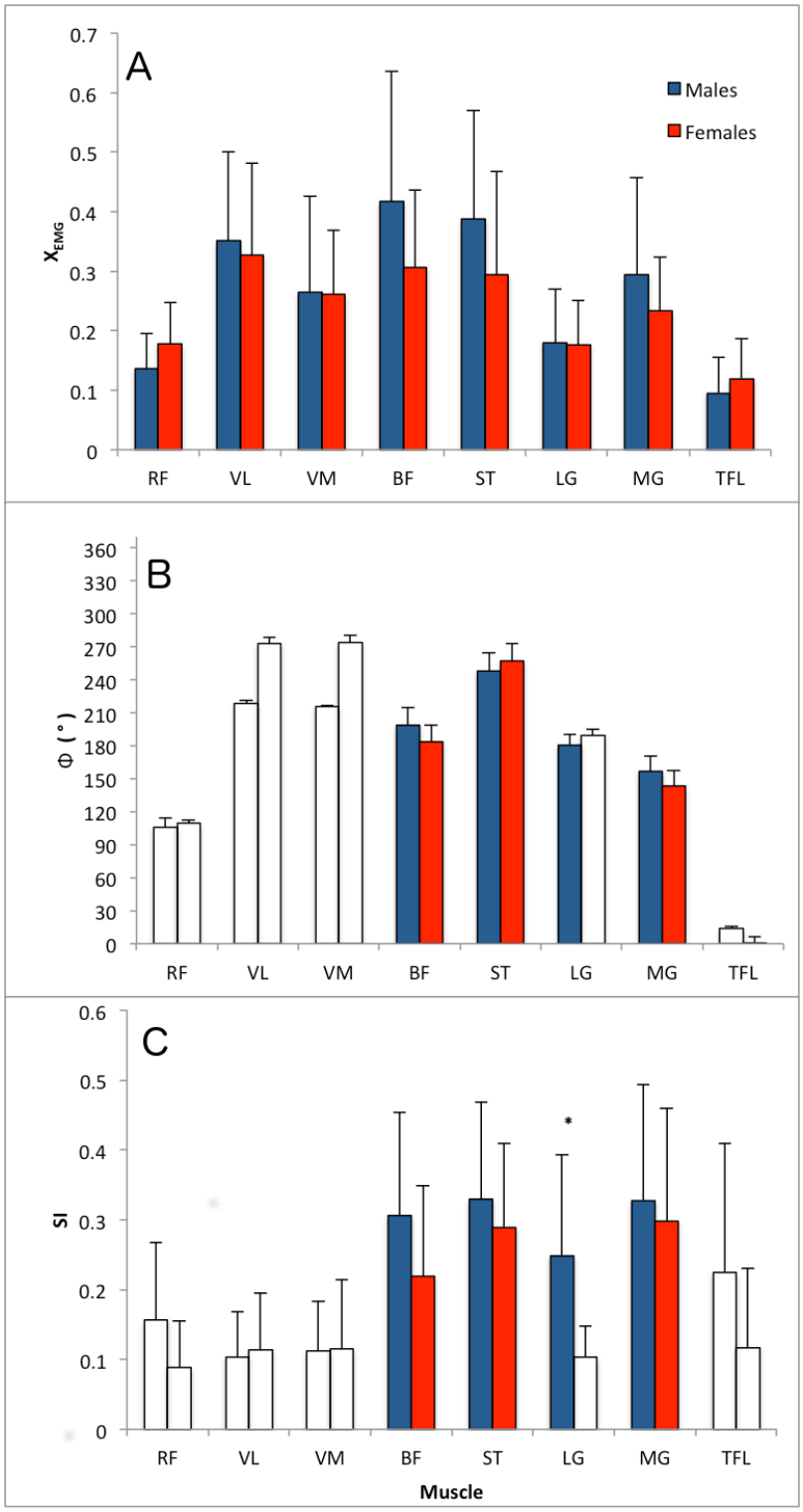

Figure 8: (A) Mean magnitude of normalised muscle activation (X_{EMG}) (i.e. 0.8 represents 80% MVIC) of eight muscles of the lower limb. Error bars represent standard deviation, (B) mean direction of muscle activation (ϕ) in degrees Error bars represent *r* for variability, (C) Specificity Indices (SI). Error bars represent standard deviation. Asterisks (*) represent significant difference between sexes ($p<0.05$). *Note: Muscles demonstrating symmetrical activation patterns have ϕ and SI bars unfilled. These values should not be interpreted as meaningful.*

Reliability analysis: ICCs for mean muscle magnitude of VL in females, TFL in males, and RF, VM, BF, ST, LG, and MG in both males and females had moderate to high between-subject reliability (ICC= 0.529-958) (Table 1). Low SEM values indicated reliable results for all muscles (0.037-0.137) (Table 1).

Table 1: Intra-Class Correlations (ICC), Confidence Intervals (CI) (95%), and Standard Error of Measurement (SEM) values in brackets of each muscle indicating variability of participant activation profiles compared to the group mean activation profile.

	RF	VL	VM	BF	ST	LG	MG	TFL
Males								
ICC	0.803 (0.037)	0.299 (0.137)	.575 (0.111)	0.928 (0.081)	0.958 (0.052)	0.757 (0.071)	0.930 (0.059)	0.529 (0.055)
Upper CI	0.933	0.760	0.854	0.975	0.986	0.917	0.976	0.839
Lower CI	0.594	-.445	0.124	0.851	0.913	0.501	0.856	0.029
Females								
ICC	0.613 (0.050)	0.782 (0.079)	0.700 (0.065)	0.866 (0.061)	0.924 (0.062)	0.569 (0.056)	0.885 (0.052)	0.502 (0.057)
Upper CI	0.868	0.925	0.898	0.954	0.974	0.853	0.961	0.830
Lower CI	0.199	0.549	0.381	0.723	0.844	0.11	0.762	-0.03

4. Discussion

The purpose of this study was to identify the stabilising role of muscles surrounding the knee in older males and females during a complex, force-dependent weight-bearing task. We achieved this by comparing neuromuscular control strategies between similarly aged participants during a task that required both groups to exert functionally relevant GRF (Smith et al., 2012) at relatively the same level of force in a highly controlled fashion. Both groups had good knee joint health and utilised similar joint positions in most directions and similar moment patterns to produce comparable normalised GRF in the lateral, anterior, and medial directions. As expected, males were stronger than females explaining their greater absolute GRF. This allowed us to reliably investigate sex differences in joint stabilisation strategies used by older adults. By using an isometric direction-dependent protocol, we decreased the complex biomechanical factors that occur during dynamic tasks and were able to link knee joint muscle activation

strategies in various directions with the external forces they produce. We hypothesised that females would have more general joint stabilisers than males due to increased muscular activation and reduced specificity and that females would have greater quadriceps activation specifically. Results supported our hypotheses in part, as females had greater X_{EMG} of RF. However, they also had lower BF X_{EMG}. SI of LG was significantly less in females and along with a negative test of symmetry, resulted in females having one more general joint stabiliser than males. Based on our polar plot analysis, we suggest fundamental stabilisation strategies in healthy older adults include: LG in females, RF, VM, VL, and TFL in males and females act as general joint stabilisers, LG in males, BF and MG in males and females act as specific joint stabilisers, and ST in males and females acts as a moment actuator.

ICC coefficients represented moderate-high (0.529-0.958) between-subject reliability in RF, VM, BF, ST, LG, and MG of both sexes, and in VL in females (Claiborne et al., 2008). VL in males and TFL in females had a low ICC and a negative value for the lower CI suggesting the between-subject variation was relatively small compared to the within-subject variation and therefore should not be considered a valid measure of reliability for these muscles. In these cases, SEM was used as a valid measure of between-subject reliability. SEM was low for all eight muscles and ranged from 0.037 to 0.137, suggesting our results are representative of a non-random sex-based neuromuscular control strategy.

Older adults produced less medial and posterior normalised GRF (N/kg) than our previously reported young adults (0.25 compared to 0.50, 0.35 compared to 0.51) (Flaxman et al., 2014), suggesting the ability to produce force in these directions is

reduced in older adults, more notably in the medial direction. Descriptively, during the protocol, participants commented that medial targets were more difficult to match than lateral targets, and that matching targets with a combination of medial and posterior loading were the most difficult. Along with less force production in these directions, was greater normalised activation of the hamstrings. Therefore, we suggest increased muscular effort utilised by older adults may be a compensatory mechanism for the reduced strength (Hortobagyi et al., 1995) and neuromuscular control that occurs with aging (Madhavan et al., 2009).

BF's increased activation in the medial direction suggests its role in joint stabilisation is most active during medial force production rather than the expected posterior-lateral direction, which would produce extension and abduction moments in accordance to the direction of its MAO. This strategy may be a mechanism to stabilise the knee joint by counteracting knee adduction moments, reducing medial joint loading (Kumar et al., 2013) that can be harmful to joint integrity. This may be a protective strategy as large knee adduction moments have been linked to OA development and progression (Miyazaki et al., 2002). Furthermore, males' used greater BF activation to stabilise the lower limb despite having greater peak knee flexion torque than females. This suggests males rely more on the BF for joint stabilisation in the medial direction. Hamstring activation is important, as this muscle group is synergistic to the ACL and provides posterior tibial shear force, limiting the ACL loading that is attributable to anterior tibial translation (MacWilliams et al., 1999). Greater hamstring activation in females with ACL repairs compared to healthy controls has been suggested to be a protective mechanism to decrease the anterior shear loads on the knee (Tsai et al., 2012).

Therefore, this strategy, not reported in our healthy, young adults, may also be a protective mechanism that healthy males utilise to increase joint stability and to promote healthy joint loading as they age. Understanding that males utilise greater BF activation, despite having greater knee flexion strength, suggests that females are unable to achieve, or need to be trained to achieve, the level of BF activation required to maintain stability. This increased BF activation may provide healthy joint loading during weight-bearing tasks by increasing the balance between quadriceps and hamstrings however; future longitudinal research is necessary to further investigate the impact of this pattern on joint health. Our data suggests that females with muscle weakness are unable to utilise their BF sufficiently, which would lead to imbalanced joint loading and may increase their risk of developing OA. As such, our results indicate that improving this muscular balance could be a target for prophylactic intervention.

As expected, females produced significantly less absolute peak torque production for knee extension, knee flexion, ankle plantar flexion, and hip abduction corresponding to significantly less absolute GRF at all target directions. The greater RF activity in females can be attributed to quadriceps weakness (Segal et al., 2010) even after accounting for females' reduced muscle volume (Slemenda et al., 1998). These studies suggest that quadriceps weakness is a risk factor for the onset of OA symptoms in females. However, their role as general stabilisers along with their increased activation implies these muscles have greater contributions to joint stability in females. Therefore, the increased activation of the quadriceps in a symmetrical pattern provides a stable joint from which ST, a moment actuator, can produce force in the posterior direction. It also

appears that females increased RF activity in the posterior direction as a mechanism to counteract the high extensor moment at the hip.

Interestingly, males had significantly greater hip extension moments and small knee flexion moments compared to female's small decreasing knee extension moment when producing the required GRF in the medial-posterior direction. This suggests the sex differences in activation strategy impact this variable's influence on joint load distribution. Further investigation into this finding is warranted to quantify its impact on knee joint loading.

In addition to limitations addressed previously (Flaxman et al., 2012, Flaxman et al., 2014, Smith et al. 2012), our inclusion criteria for age was broad, "over 50" so as to reach a sufficient number of participants in an allotted time. Therefore, participants' ages ranged from 54-71years old. We accept that a decrease in muscle strength comes with aging (Hortobagyi et al., 1995); however, forces were normalised to each individual's maximum ability, and all participants included in the analysis had sufficient strength and control to meet our task demands. Our analysis on 36 older adults with the ability to complete our protocol suggests our results are representative of a healthy, older population with good neuromuscular control. As this is a cohort study, further research is necessary to determine if these activation patterns represent strategies that support healthy joint loading. That said, since the majority of males in this sample were over 60, we suggest males demonstrated healthy strategies while the strategies; since the majority of females were in their 50s and may still develop OA, we can not draw the same conclusion.

5. Conclusion

Our study presents fundamental roles of joint stabilisation of knee joint muscles during isometric weight-bearing direction-dependent loading in older adults. We suggest fundamental sex differences in stabilisation strategies include greater RF activation, less BF activation, and less specific activation patterns of RF and LG in females compared to males. Furthermore, older females demonstrated increased RF activation and reduced specificity compared to younger healthy females suggesting while activation patterns and muscle roles remain, increased activation and reduced specificity progress with age leading to muscles activating in more symmetrical patterns contributing to general joint stability. BF's role as a specific stabiliser resulted in part from its increased activation in the medial direction, which results suggest may be a mechanism used to improve joint stability and counteract knee adduction moments, which was a strategy also seen in healthy younger males. As older, healthy females were unable to activate their BF to the same extent, this may increase their risk for joint instability and negative joint loading patterns. Rehabilitation programs can use these findings to focus on RF, BF, and LG muscles as they provide stability to the joint, yet have altered strategies in older females. Furthermore, improving females' hamstring function and quadriceps-hamstrings muscle coordination may reduce harmful joint loading and improve knee stability while bearing weight.

Conflicts of Interest

None declared.

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ARTICLE 2: NEUROMUSCULAR ADAPTATIONS IN OLDER MALES AND FEMALES WITH KNEE OSTEOARTHRITIS DURING WEIGHT-BEARING FORCE CONTROL

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Abstract

Objective: Muscular stabilisation strategies during activities of daily living alter in the presence of knee osteoarthritis (OA). However, it remains difficult to determine individual muscle roles to joint stabilisation due to the multiple biomechanical factors of dynamic tasks. The primary aim of this study was to identify sex differences in OA-affected adults, and within-sex differences between healthy and OA-affected adults in lower limb muscular activation patterns and to determine individual muscle roles to providing joint stability associated with knee OA.

Methods: Fifty OA (29 females) and forty-nine controls (27 females) were recruited to participate in a force matching protocol. This required participants to modulate both the direction and magnitude of their ground reaction forces (GRF) along the horizontal plane while maintaining constant joint position, and 50%±5% body mass. Electromyography, GRF, and kinematics were recorded. A test of asymmetry determined the activation pattern of each muscle and was supported by its respective specificity index (SI) and mean direction of activity (ϕ) and used to determine each muscle's role.

Results: Males and females with OA utilised greater rectus femoris mean magnitude than healthy participants of the same sex ($p=0.016$, 0.072). Females with OA had significantly greater biceps femoris (BF) mean magnitude than female controls ($p=0.041$) and significantly greater medial gastrocnemius mean magnitude than female controls ($p=0.031$) and males with OA ($p=0.020$). SI was significantly greater in males with OA compared to females with OA in BF ($p=0.013$). Lateral gastrocnemius SI was greatest in male controls and corresponded with an asymmetrical activation pattern and $\phi=181°$

leading to its role as a specific stabiliser contrasting the role as a general stabiliser in all other groups. All other muscles had the same role in all groups.

Conclusion: We have identified fundamental differences in muscular stabilisation strategies in older adults with OA and these strategies may influence long-term joint integrity. Our findings can be used to develop muscle-specific training strategies to improve joint stability in this population.

INTRODUCTION

Neuromuscular adaptations associated with aging, such as increased normalised quadriceps and hamstring activation, reduced muscle strength (Hortobagyi et al., 2005), and reduced capacity for muscular control (Herzog et al., 2003), are further exaggerated in older adults with knee osteoarthritis (OA) (Hubley-Kozey et al., 2009; Rutherford et al., 2013) and therefore are believed to be risk factors for the onset of this chronic condition. Altered activation strategies are suggested to improve joint stability in this population however these alterations may negatively alter joint loading and be detrimental to joint integrity (Lewek et al., 2005; Schmitt & Rudolph, 2007). Understanding the roles muscles play in providing stability to the joint can prove to be useful in determining prophylactic rehabilitation strategies focused on muscles with the greatest contribution to joint stability.

An isometric force matching protocol, with less biomechanical complexities than dynamic tasks, provides a static environment to investigate muscular stabilisation strategies. Sex differences in neuromuscular adaptations to stabilise the knee joint during isometric force matching tasks have been reported in younger, healthy adults (Flaxman et al., 2014; Krishnan et al., 2008) and in older, healthy adults (Bigham et al., *unpublished*, 2014a). However, isometric stabilisation strategies during a force matching task and the defining of muscle roles as they contribute to joint stabilisation have yet to be fully explored in older adults with OA. Previous studies investigating muscular activation strategies during dynamic tasks suggest altered strategies, such as increased hamstrings and quadriceps activation compared to age-matched controls, are associated with OA (Hubley-Kozey et al., 2009; Rutherford et al., 2013, Schmitt & Rudolph, 2007). As

healthy, older females utilise greater rectus femoris (RF) activation and less hamstring activation than males during isometric tasks (Bigham et al., *upublished,* 2014a), this may be an influential factor that suggests normalised muscle activation strategies impact joint loading and therefore play a role in understanding the prominent OA prevalence in this sex. This increased RF activation corresponded with greater quadriceps inhibition in those with OA and healthy females compared to males with healthy knees (Bigham et al., *unpublished,* 2014b). Therefore, maximum voluntary isometric contraction (MVIC), the method commonly used to normalize EMG data in this population, does not represent these populations "true" maximum muscle activation and may be the cause of the increased RF activation. This suggests there may not be a significant difference if "true" MVIC data was used to normalize the EMG data. No significant differences were found in knee flexor strength deficits suggesting the decreased hamstring activation is a true representation of an activation strategy males use that females are unable to achieve. This may improve joint loading in males decreasing risk in OA development in this sex. As the majority of males in the sample were over 60, and the majority of females were in their 50s, we suggest males demonstrated a "gold standard" for both males and females. A longitudinal study is necessary to determine if the sex differences in activation patterns represent strategies that support healthy joint loading or lead to joint degeneration.

Radiographic features of OA, such as osteophytes, narrowing of joint cartilage, sclerosis, and altered shape of bone ends (Kellgren & Lawrence, 1957) affect joint integrity by altering contact surface area between the femur and tibia and increasing maximum contact stress (Segal et al., 2009). This change in joint loading may further progress degeneration of joint cartilage and lead to adaptations in joint stabilisation

strategies. Additionally, increased mean activation of muscles to stabilise the joint may reduce the directional specificity of those muscles' activation pattern (Bigham et al., *unpublished*, 2014a). Surrounding muscles increase activation to achieve task demands, such as ground reaction force (GRF) control, and as a result, muscles display more symmetrical activation patterns and may have greater contributions to joint loads (Flaxman et al., 2014). In the case of older adults, this increased activation may be a response to the age-associated loss of muscle strength that is present before, and exaggerated following OA development (Hortobagyi et al., 2005).

Muscle weakness may also result in a diminished capacity for muscular control (Herzog et al., 2003) and be a pre-cursor to OA due to the resulting altered joint loading (Herzog et al., 2003; Herzog & Longino, 2007). For example, following a Botulinum type-A toxin injection to rabbit knee extensors to reduce muscle mass, a loss of 68% quadriceps strength was associated altered joint loading that resulted in reddening of the articular joint margin on the tibial plateau, one of the first sign of osteoarthritis (Herzog & Longino, 2007). Older females generally have weaker quadriceps and hamstrings muscle strength compared to age-matched males and lower quadriceps strength specifically has been considered a risk factor for the onset of OA in females (Slemenda et al., 1997). It has been associated with increased pain (Glass et al., 2013), increased joint space narrowing, and decreased functional abilities (Segal et al., 2010). This suggests reduced muscle strength negatively impacts joint loading leading to symptoms and development of OA. Females with radiographic OA had 18% (0.47 versus 0.57 ft-lb/kg) (Slemenda et al., 1998) and 22% (Palmieri-Smith et al., 2010) less quadriceps strength (normalized to body mass) compared to female controls with healthy knees. Meanwhile,

previous reports of strengthening interventions in older adults have resulted in improved strength, voluntary activation, and function (Hurley & Scott, 1998) suggesting that regardless of degree of knee extensor weakness, increasing strength is expected to reduce risk of OA-development.

While it remains difficult to determine timing of the onset and progression of OA, understanding muscular contribution to knee joint stabilisation may provide insight into which muscles can be targeted to improve joint stability, potentially as a prophylactic means of slowing the degenerative process. We have developed and validated a test that allows us to determine joint stabilisation strategies during physiologically relevant weight-bearing conditions (Flaxman et al., 2012; Flaxman et al., 2014; Smith et al., 2012). By identifying alterations in muscle roles and activation strategies in response to negative changes in joint surfaces, our goal is to advance the understanding of muscle stabilisation strategies utilised by males and females with OA. Therefore, the objective of this study was to use our weight-bearing, direction-dependent protocol to identify sex differences in OA-affected adults, and within-sex differences between healthy and OA-affected adults in lower limb muscular activation patterns and to determine muscle stabilisation roles associated with OA. We hypothesised that OA-affected adults would have greater EMG activity, specifically of the quadriceps, and reduced specificity than healthy, older adults respective of sex, and to a greater extent in females with OA compared to males with OA.

PATIENTS AND METHODS

Participants. Forty-nine healthy controls (OC) (27 females, 22 males) and fifty adults with knee osteoarthritis (OA) (29 females, 21 males) were recruited from the Ottawa area between 2011 and 2014. Inclusion criteria for both groups included: over the age of fifty and physically active at least two days a week. Exclusion criteria for both groups included: a significant lower limb injury (i.e. ligament rupture), a lower limb fracture, a lower extremity motor nerve lesion, corticosteroid injection, and/or the presence of a knee joint effusion, within six months prior to participation; diabetes; BMI $\geq 35 kg/m^2$; and any other physical or neurological impairment that could affect the results of this study. Healthy controls were excluded if their Knee Osteoarthritis and injury Outcome Score (KOOS) (Roos et al., 1998) subscale scores classified them as having symptomatic OA (pain ≤86.1, symptoms ≤85.7, function/daily living (ADL) ≤86.6, function/sports and recreation (Sports) ≤85 and quality of life (QoL) ≤87.5) (Lohmander et al., 2004). Males and females with OA were previously diagnosed with radiographic knee osteoarthritis by a general practitioner. The University of Ottawa Research Ethics Board approved this study and all participants provided written informed consent prior to data collection. Of the 99 recruited, 33 were excluded (Table 2). Thus, 66 participants completed the protocol and were included in the data analysis.

Assessment of knee joint function and physical activity levels. All participants filled out the KOOS and reported the frequency, intensity, type, and time per week of physical activity they engaged in. The KOOS rates symptoms, pain, ADL, Sports, and QoL on a Likert scale of 0-4. Scores were converted to a scale of 0-100 (worst-best) (Roos et al. 1998). KOOS is a valid and reliable tool for measuring symptoms in older populations with OA (Roos & Lohmander, 2003).

Kinetics, kinematics, and electromyography (EMG). Participants were fitted with a black spandex suit and then lower limb anthropometrics were recorded. Forty-five reflective markers were placed on each participant according to a modified Plug-in-Gait model (Beaulieu et al., 2010). Marker trajectories were recorded by a ten-camera infrared motion analysis system (Vicon MX-13, Oxford Metrics, Oxford, UK) at 200Hz and ground reaction forces (GRF) from a force platform (FP4060-08, Bertec Corporation, Columbus, OH) were recorded at 1000Hz using *Nexus* software (v.1.7, Oxford Metrics, Oxford, UK). The raw 3D marker trajectories and GRF were filtered using a 4^{th} order zero-lag Butterworth filter with a cut-off frequency of 20Hz. Joint moments were calculated using inverse dynamics and joint angles were calculated in accordance with the modified Plug-in Gait model in *Nexus* software (v.1.7, Oxford Metrics, Oxford, UK). Bipolar surface electrodes (DS-B04, Bagnoli16, Delsys Inc., Boston, MA) were placed on eight muscles of the test limb (defined as: the leg participant would use to kick a soccer ball as far as possible for OC and participants with bilateral OA, and affected limb for participants with unilateral OA): rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), semitendinosus (ST), lateral gastrocnemius (LG), medial gastrocnemius (MG), and tensor fascia latae (TFL) according to SENIAM guidelines (Hermens et al., 2000). EMG was sampled at 1000Hz, amplified by a gain of 1000, band-pass filtered at 20-450Hz using a 16-bit A/D conversion board (NI PCI 6229, National Instruments Corp., Austin, TX), and recorded in a custom-made *Matlab* application (2007b, Mathworks, Natick, MA).

Maximum voluntary isometric contractions (MVICs). Participants performed a series of MVICs using an isokinetic dynamometer (850-000, Biodex, Shirley, NY) to

normalise EMG data from the target match protocol and to determine peak torque for four lower limb movements. Three repetitions of isometric knee extension, knee flexion, and ankle plantar flexion were completed while seated with hip, knee, and ankle joints at 30° flexion, 30° flexion, and 10° ankle plantar flexion, respectively. Hip abduction was completed standing in a neutral position (hip and knee at 0°). Torque and EMG were collected and processed in a custom-made *Labview* application (v.8.20, National Instruments Corp., Austin, TX). EMG data from MVICs were full wave rectified, and both EMG and torque data had bias removed and were filtered with a 4^{th} order Butterworth dual low-pass filter (6Hz). The peak EMG/torque value was determined as the maximum value for each muscle/movement during MVIC data collection. The mean of a 50ms range about the peak EMG/torque value was used as each muscle/movement's MVIC value.

Target Matching Protocol. Protocol details have been previously described (Flaxman et al., 2012, 2014; Smith et al., 2012). In short, each participant's test foot was secured in a water-ski boot attached to a force platform (Fig. 9). Participants were required to maintain joint positions of 30° hip flexion, 30° knee flexion, and 10° ankle plantar flexion while modifying GRF to match a cursor to a target on a screen in front of them. Maximum isometric forces were collected in medial/lateral (±Fx) and anterior/posterior (±Fy) loading directions while maintaining 50%±5% body mass (BM) (inferior/superior loads (±Fz)) on the test limb. GRF controlled the cursor that moved with three degrees-of-freedom: ±Fx moving the cursor left/right, ±Fy moving the cursor upwards/downwards, and ±Fz making the cursor smaller/larger (i.e., controlling the percent BM applied to the ground). These forces were used to normalise the task

demands required to successfully match each target location. Targets at 0°, 90°, 180°, and 270°, represented lateral, anterior, medial, and posterior loading directions, respectively. A successful trial required 30%±3.6% peak load in the ±Fx and ±Fy directions while maintaining 50%±5% BM. Twelve targets spaced every 30° about a circular trajectory appeared on the screen in a randomized order. Specified GRF (cursor within the limits of the target) were held for a half-second triggering synchronised data collection of surface EMG, kinematics, and GRF for four seconds (three-and-a-half seconds prior to the matched target, and a half-second the target was matched). A minimum of thirty seconds rest was given between each successful trial to limit fatigue. A practice trial of each target was completed prior to MVIC data collection. The protocol was repeated following MVICs and each participant completed three trials of each target.

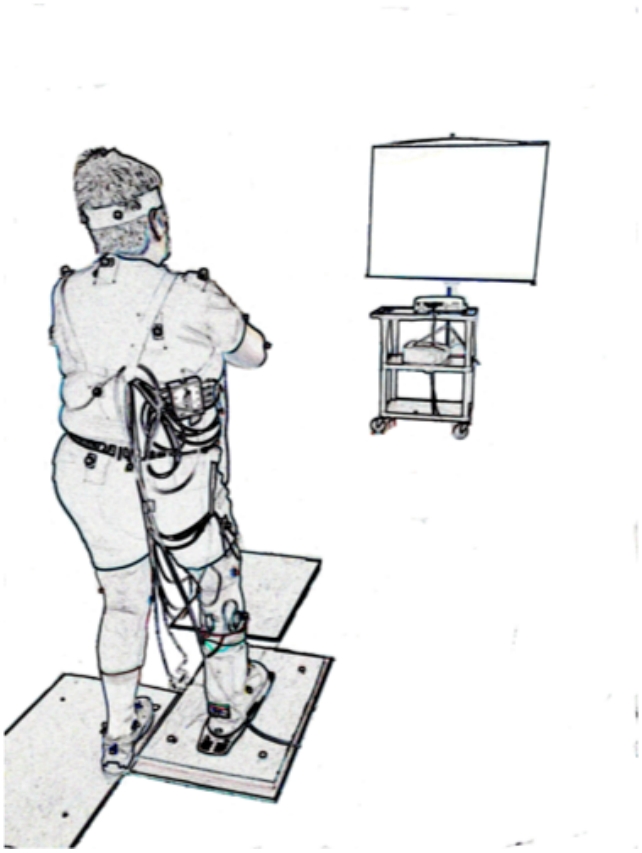

Figure 9: Laboratory setup with participant's test foot secured into a ski-boot attached to a force platform with a screen approximately 3m in front of them.

Target Match Data Analysis. Target match EMG data was full wave rectified, bias removed, and filtered using a 4th order Butterworth dual low-pass filter (6Hz) and was normalised to MVIC data in a custom-made *Matlab* application (2007b, Mathworks, Natick, MA). The half-second of normalised surface EMG were time-averaged and then ensemble-averaged across successful trials and were represented as an EMG vector (EMG_i) for each direction. EMG_i magnitude were plotted in polar coordinates to visually represent muscle activation patterns (Dewald et al., 1995). The mean magnitude of muscle activity (X_{EMG}) was computed for each of the eight muscles by averaging the normalised EMG_i from every target location. Methods by Curray (1956) were used to quantitatively describe asymmetry about the polar plot indicating if muscle activation was greater in one direction relative to another, or relatively equal in all directions. For muscles with asymmetrical activation, the mean direction of muscle activity (ϕ) and specificity index (SI) were calculated to describe the direction and degree of focus the muscle's activation had (Dewald et al., 1995; Williams et al., 2003).

Muscle stabilisation roles were defined as: *general joint stabiliser, specific joint stabiliser,* and *moment actuator* (Flaxman et al, 2012). A general joint stabiliser was defined as having a symmetrical activation pattern (activation is present and relatively equal in all target directions), relatively low SI, and a non-interpretable ϕ. A specific joint stabiliser was defined as having an asymmetrical activation pattern (activation preferentially in specific GRF directions) supported by a relatively high SI and its ϕ in a direction opposing its moment arm orientation (i.e.: a role not generally associated with that muscle based on its line of action). A moment actuator was defined as having asymmetrical activation pattern supported by a relatively high SI and its ϕ in the direction

of its moment arm orientation.

Statistical analysis. Analyses were completed to determine differences between sexes in OA-affected adults (male OA, female OA) and between groups respective of sex (male OA, male OC; female OA, female OC). Group differences in age, BMI, KOOS, absolute and normalised peak torque production, X_{EMG}, and SI were determined using one-way analyses of variance (ANOVAs) with three planned comparisons. Between group differences in KOOS subscales were determined for each pair using mixed between-within ANOVAs (2x5). Multivariate analyses of variance (MANOVA) were used to determine group differences in joint angles and moments at each target direction. An adjusted alpha level of 0.017 was used as three plane-dependent variables were extracted for each joint. A MANOVA was used to determine group mean differences of absolute GRF in every direction and normalised GRF in the lateral, anterior, medial, and posterior directions in the *x* and *y* planes at each direction. An adjusted alpha level of 0.025 was used for GRF to account for the two dependent force plate loading axes (*x, y*). Mixed model ANOVAs (2x12) were used to determine group differences in each muscle's magnitude by target direction. In the case of significance, post hoc evaluations were conducted with one-way ANOVAs with planned comparisons and independent t-tests for each direction to determine if a between-group difference occurred in specific loading directions. Watson-Williams tests were used to determine group differences in ϕ for each muscle. A Pearson's correlation analysis was used to determine the strength of the linear relationship between the age of OA-affected adults and their KOOS scores. An adjusted alpha level of 0.025 was used for all mixed model ANOVA tests and Watson-Williams test to account for female OA and male OA each being used in two between-group

analyses. An alpha level of 0.05 was considered significant for all other analyses. Intra-class correlation coefficients ($ICC_{(2, k)}$) (Portney & Watkins, 2000; Shrout & Fleiss, 1979) and standard error of measurement (SEM) (Portney & Watkins, 2000) were used to evaluate between-subject reliability of muscle activation profiles compared to the mean profile within each group. Watson-Williams tests were run in PAleontological STatistics (PAST) (Hammer et al., 2001) and all other analyses were completed in SPSS (v. 21.0, IBM, Chicago, IL).

RESULTS

Participants and demographics: 66 participants completed the protocol and their data was used in the analyses. Not all participants were able to successfully match each target within our required range for half a second three times. As our protocol has proven between-trial reliability (Smith et al., 2012), two healthy males, one healthy female, and two males with OA that successfully matched at least one successful trial within our required GRF range were included in the analysis. A custom-made *Matlab* application (2010b, Mathworks, Natick, MA) was developed to determine if skipped steps, those not within the required GRF range, were within an acceptable range of 30%±10% Fx and Fy, and 50%±5% BM. One healthy male, two males with OA, and two females with OA had trials within this range that led to a minimum of one trial of each target, therefore, they were included in the analyses. Participants who were unsuccessful at completing the protocol were unable to match each target at least once. Participants who withdrew from the protocol did not complete the practice trials or asked to stop before completion of at least one trial of each target during the testing protocol. A summary of those excluded,

participant demographics, and KOOS scores are presented in Table 2. Peak torque production, mean joint angles, and mean normalised GRF are presented in Table 3. To summarise, all participants were similarly aged and OA-affected adults had higher mean BMI and significantly lower KOOS scores as expected. Male OA had significantly greater absolute hip abduction torque compared to female OA and significantly less absolute peak knee extensor torque compared to male OC ($p<0.05$). Normalised peak knee flexion torque was significantly less in female OA compared to male OA and normalised peak knee extension torque was significantly less in female OA compared to female OC and ($p<0.05$). While male OA had a greater mean ankle flexion angle than male OC, all other groups had similar mean joint sagittal-plane angles during testing to produce comparable normalised GRF (N/kg).

Following a post-hoc analysis to determine which direction(s) the ankle sagittal-plane angle differed in between male OA and male OC, a covariate analysis was run on each muscle at those directions and determined a potential effect for ankle angle at targets 240° (male OA: 10.3°; male OC: 3.6°) and 300° (male OA: 11.4°; male OC: 4.9°) for the RF ($p<0.05$), however this effect did not lead to significant differences in activation levels between the sexes for these targets.

A second post-hoc analysis indicated female OA produced significantly less than male OA at directions 150°-330° in the y-axis, and 210° and 240° in the x-axis and that male OA produced significantly less absolute GRF in the y- axis in directions 60°, 90°, and 210°-330° compared to male OC.

Table 2: Group mean ± standard deviation of participant demographics and KOOS scores.

Variable	OA: Males	OA: Females	OC: Males	OC: Females
Withdrew/ Unsuccessful	2: withdrew 3: unsuccessful	4: withdrew 11: unsuccessful	2: withdrew 1: unsuccessful	2: withdrew 8: unsuccessful
Included	n=16	n=14	n=19	n=17

Age (years)	65± 8	64± 6	64± 8	61± 5
BMI (kg/m^2)	25.6± 3.7	26.6± 2.5	26.0± 4.1	23.0± 2.6
KOOS				
Symptoms	71.9± 15.5	65.1± 15.0	94.2± 6.5	93.3± 6.8
Pain	73.8± 16.0	72.5± 16.6	97.5± 3.1	96.7± 3.6
ADL	83.1± 14.2	80.7± 12.8	98.4± 2.9	98.4± 3.2
Sports	59.7± 25.9	55.3± 13.5	95.8± 8.6	94.3± 8.3
QoL	52.7± 20.0	45.5± 17.9	95.1± 7.7	93.0± 12.7
Total	*68.6± 15.0*	*64.1± 11.5*	*96.1± 4.3*	*95.2± 5.4*

Table 3: Group mean ± standard deviation of participant absolute (Nm) and normalised (Nm/kg) peak torque production (PF=plantar flexion), sagittal-plane joint angles, and normalised GRF (N/kg) during successful matches, and number of participants with unilateral OA. Asterisks (*) represent OA groups significantly different than OC groups; ♯ represents male OA significantly different than male OC; ♮ represents female OA significantly different than female OC.

Variable	OA: Males	OA: Females	OC: Males	OC: Females	P value
Absolute Peak Torque (Nm)					
Knee Extension	93.0± 22.7	76.4± 24.8	116.3± 27.9	81.7± 20.1	p=0.006#
Knee Flexion	62.5± 19.8	51.4± 20.2	65.7± 17.4	49.3± 12.7	
Ankle PF	67.9± 19.0	57.1± 20.2	75.2± 21.0	53.3± 18.5	
Hip Abduction	65.2± 15.8	51.2± 15.2	66.0± 18.6	51.3± 14.1	p=0.021*
Normalised Peak Torque (Nm/kg)					
Knee Extension	1.27± 0.35	1.05± 0.30	1.49± 0.37	1.38± 0.31	p=0.010♮
Knee Flexion	0.86± 0.27	0.70± 0.24	0.83± 0.21	0.83± 0.16	
Ankle PF	0.94± 0.31	0.80± 0.28	0.95± 0.27	0.92± 0.35	
Hip Abduction	0.90± 0.26	0.71± 0.18	0.84± 0.24	0.77± 0.36	
Joint Flexion Angles (°)					
Hip	25.5± 11.1	26.3± 10.6	23.2± 8.0	24.8± 10.0	
Knee	18.4± 8.3	19.2± 7.8	17.6± 5.5	20.0± 7.1	
Ankle	11.2± 10.9	9.0± 6.2	4.6± 5.9	7.8± 5.5	p<0.001#
GRF (N/kg)					
+Fx (0°)	0.600± 0.187	0.518± 0.175	0.537± 0.103	0.548± 0.119	
-Fy (90°)	0.548± 0.138	0.505± 0.182	0.525± 0.116	0.438± 0.117	
-Fx (180°)	0.321± 0.136	0.220± 0.098	0.280± 0.124	0.212± 0.107	
+Fy (270°)	0.398± 0.119	0.310± 0.122	0.384± 0.086	0.309± 0.089	
Unilateral OA	8	6	--	--	--

KOOS: Pearson's correlation coefficient represented a significant moderate negative correlation for age and KOOS scores in the OA-affected adults (r=-0.320, p=0.009). As expected, male and female OA had significantly worse KOOS scores than male and female OC (p<0.01). ADLs score was significantly greater than all other subscales while QoL was significantly less than symptoms, pain, and ADLs (p<0.05).

Kinetics: Post-hoc analysis following significant between-group differences from the MANOVA ($p<0.017$) found female OA had significantly smaller hip adduction moments compared to male OA at all directions, smaller ankle abduction moments at 120° and 150° compared to male OA, and smaller moments compared to female OC, specifically, hip adduction at 180°, hip external rotation at 90° and 180°, knee external rotation at 120°, 180°, and 210°(Fig. 10), and ankle abduction and external rotation at 210°. All groups used large hip extensor moments (0.297-0.583) to match posterior targets and large hip adductor moments (0.216-0.529) to match medial targets (Fig. 10).

Muscular activation patterns and stabilisation roles: ICCs for muscles with asymmetrical activation patterns (BF, ST, MG) had high between-subject reliability (ICC >0.840) (Portney & Watkins, 2000) in all groups. ICCs for RF, VM, and TFL in female OA, VL, LG, and TFL in male OA, VL in male OC, and TFL in female OC had low ICCs resulting from their negative lower CI suggesting ICC is not a valid test of reliability for these muscles in older adults with and without OA for this protocol. Therefore, we used SEM as a valid indicator of reliability. Low SEM values (0.037-0.137) in all muscles signified reliable results (See: Appendix D, Table 26).

Polar plots display group mean activation patterns for each muscle (Fig. 11). MG X_{EMG} was significantly greater in female OA than both male OA ($p=0.020$) and female OC ($p=0.031$) (Fig 12A), specifically, greater than male OA in directions 30°, 120°, and 330°, and greater than female OC in directions 210°-330° ($p<0.05$). RF X_{EMG} was significantly greater in male OA compared to male OC ($p=0.016$) (Fig. 12A), specifically greater in directions 180°-60° (Fig. 11). RF X_{EMG} and BF X_{EMG} were greater in female OA compared to female OC ($p=0.072$, 0.041) (Fig. 12A). Specifically, greater normalised

RF activity in directions 180° and 210°, and greater normalised BF activity in directions 210°-330° (Fig. 11). Male and female OA and OC had similar asymmetrical activation patterns with BF, ST, and MG oriented in the medial (ϕ=192°, 206°, 199°, 184°), posterior (ϕ=260°, 256°, 248°, 257°), and anterior-medial (ϕ=161°, 178°, 157°, 144°) directions respectively ($p<0.05$), (Fig. 12B). SI for male and female OA and male and female OC, respectively, was not statistically different for ST (0.278±0.104, 0.227±0.075, 0.330±0.139, 0.289±0.120) and MG (0.252±0.158, 0.195±0.145, 0.327±0.165, 0.298±0.161) ($p>0.05$); however, SI of BF was significantly lower in female OA than male OA, respectively, (0.177±0.066, 0.273±0.123) ($p=0.013$) (Fig. 12C), indicating a more generalised activation pattern in this group. LG displayed a symmetrical pattern about the polar plot in all groups except male OC ($p>0.05$), supported with a relatively high SI (0.248±0.144) (Fig. 12C) and a ϕ=181° in this group (Fig. 12B).

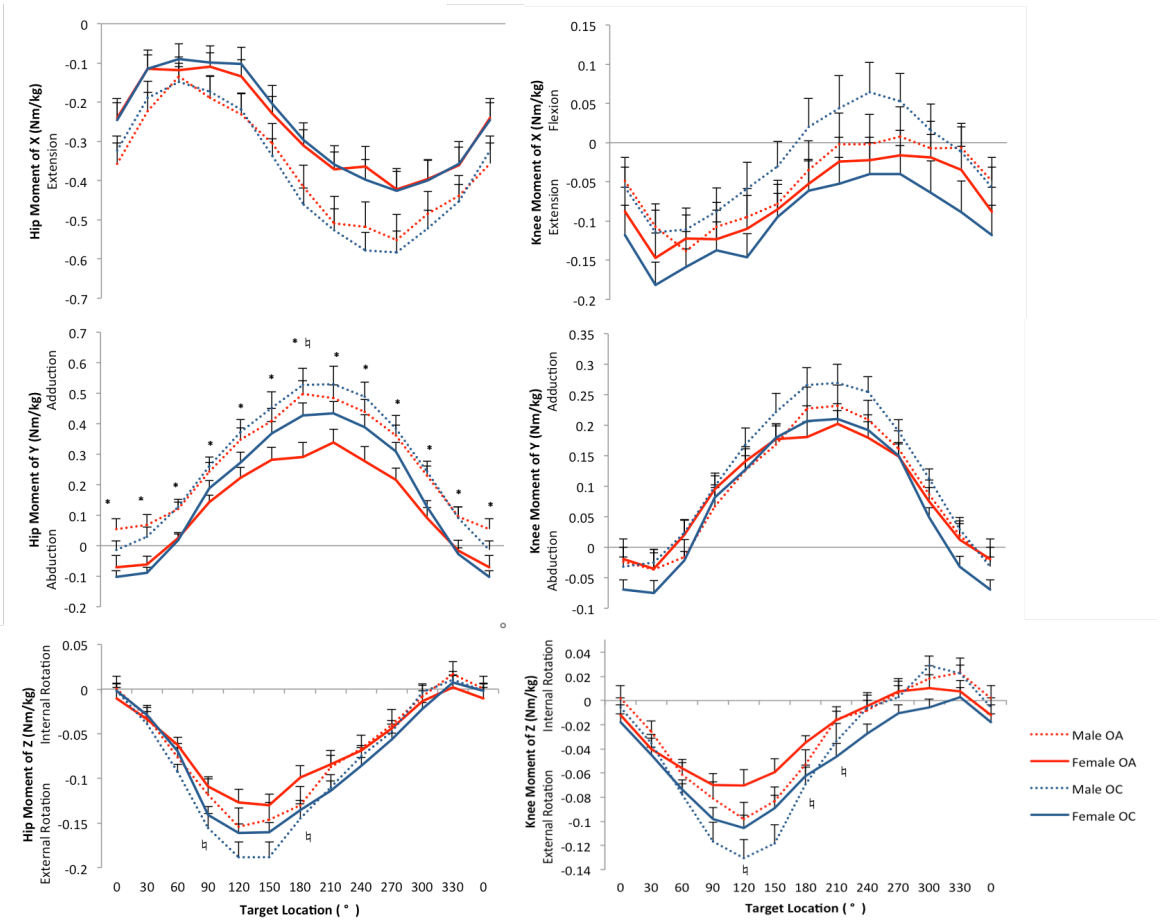

Figure 10: Group mean and standard error of the mean of the hip and knee joint moments of the (A) x-, (B) y-, and (C) z- directions in Nm/kg (normalised to BM). Values are means from moments time normalised to the half-second of a successful match in each target direction. Asterisks (*) represent male OA significantly different than female OA; ♯ represents male OA significantly different than male OC; ♮ represents female OA significantly different than female OC.

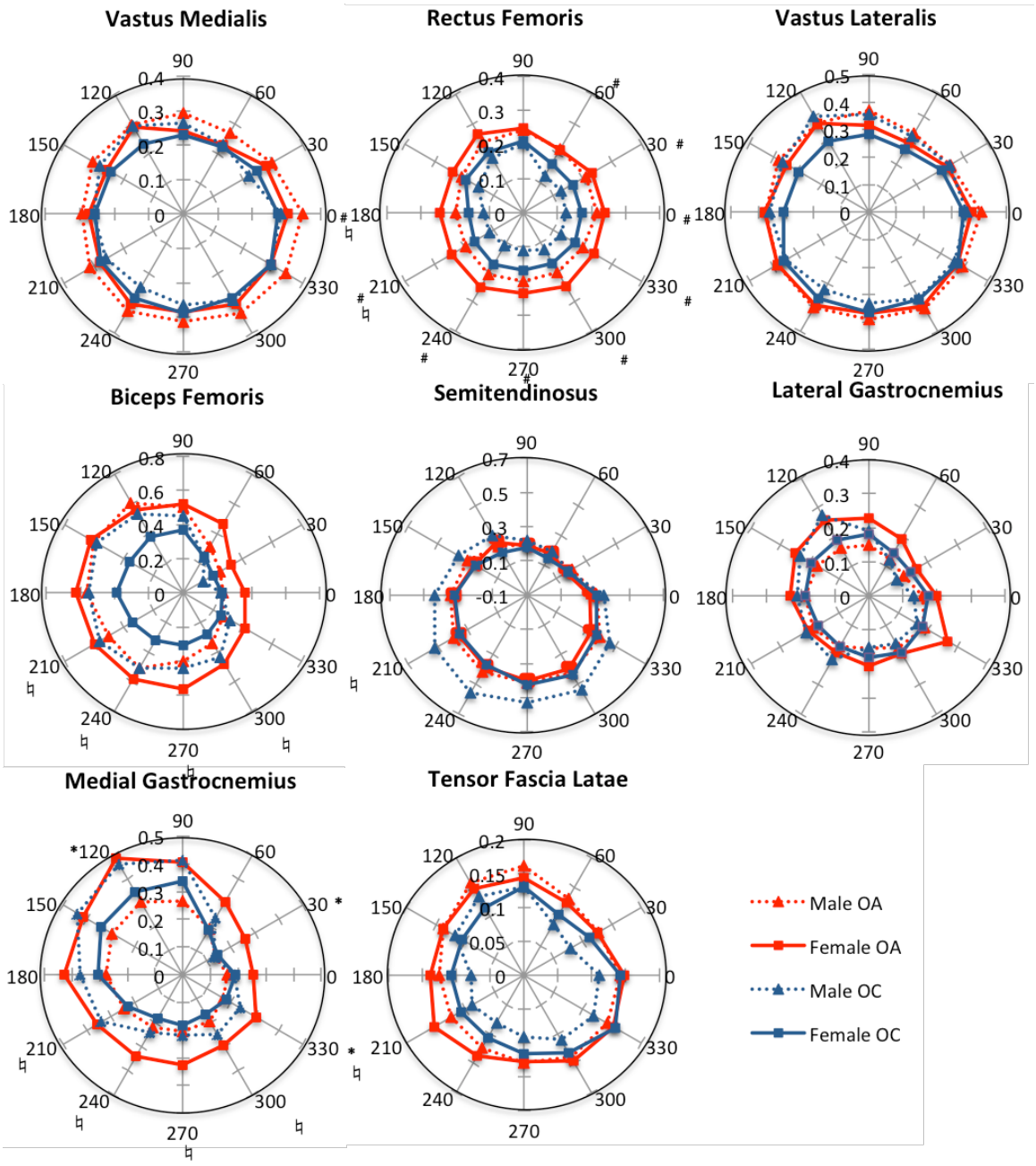

Figure 11: Polar plots of muscle activation patterns of male OC, female OC, male OA, and female OA. Number's surrounding the circular trajectory represent target location (°). Inner radius values represent normalised muscle activity at the corresponding direction. Asterisks (*) represent male OA significantly different than female OA; ♯ represents male OA significantly different than male OC; ♮ represents female OA significantly different than female OC.

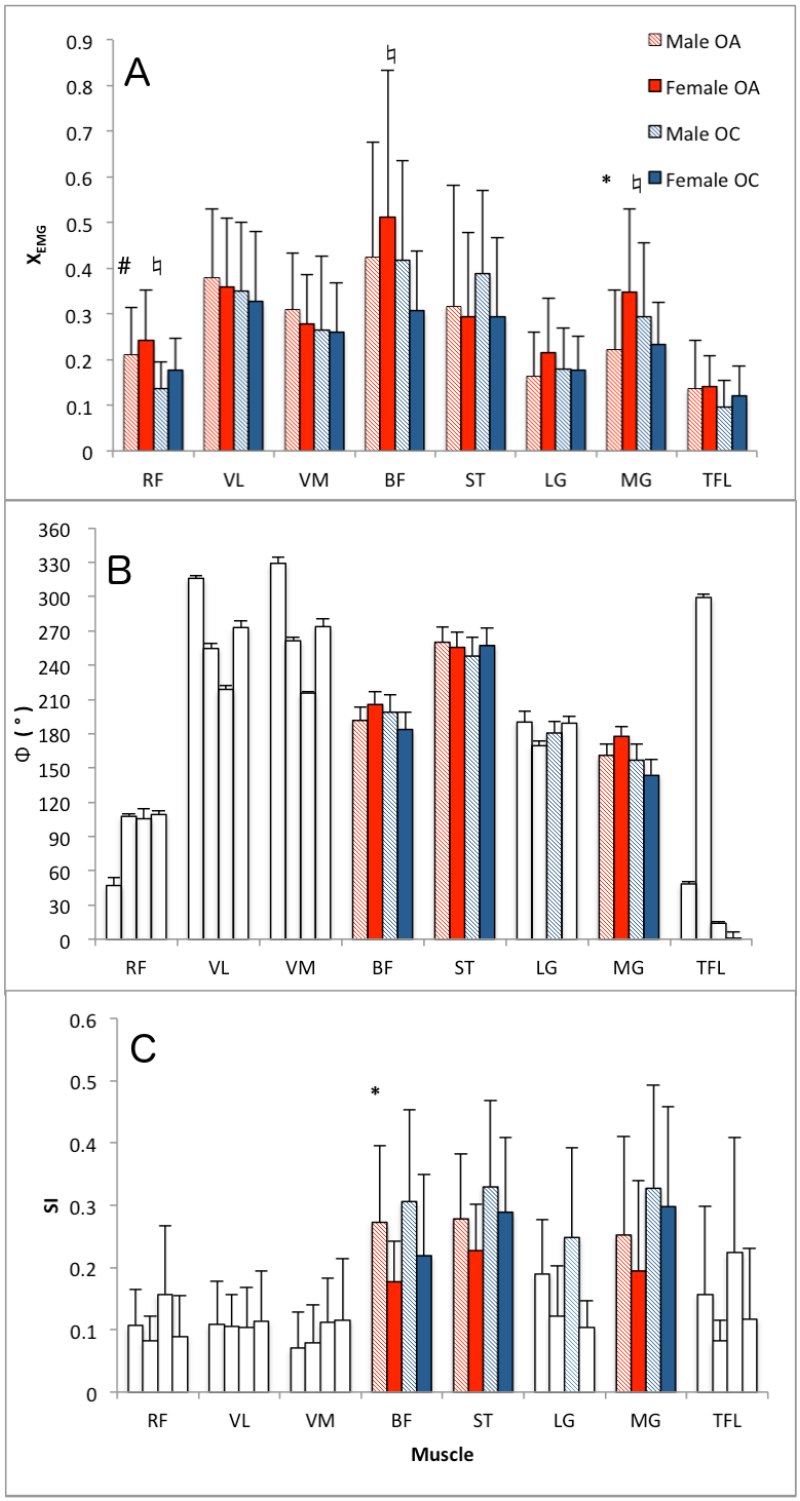

Figure 12: (A) Mean magnitude of normalised EMG activation (X_{EMG}). Error bars represent standard deviation, (B) mean direction of muscle activity (ϕ) for all eight muscles in degrees. Error bars represent *r*, (C) SI of all eight muscles. Error bars represent standard deviation. Asterisks (*) represent male OA significantly different than female OA; ♯ represents male OA significantly different than male OC; ♮ represents female OA significantly different than female OC. *Note: Unfilled bars represent muscles with symmetrical activation patterns (p>0.05) and should not be interpreted as meaningful.*

DISCUSSION

This study advanced the understanding of muscle stabilisation strategies used by males and females with OA while determining roles individual muscles play in providing isometric joint stabilisation. Our groups were similarly aged and used similar sagittal-plane joint angles at the hip and knee to produce functionally relevant GRF (Smith et al., 2012) at relatively the same level of force. KOOS scores were comparable to those previously reported (Heiden et al., 2009a; Kumar et al., 2013) and were significantly less in OA participants as expected. Our results support our hypotheses in part, male and female OA used greater normalised RF activity than controls of the same sex. Interestingly, female OA used greater normalised BF activity than female OC as well as greater MG activity than both female OC and male OA. Females had lower muscle specificity compared to males, significantly lower in BF in female OA compared to male OA.

Our findings suggest the classification of RF, VL, VM, and TFL as general joint stabilisers; BF and MG as specific joint stabilisers; and ST as a moment actuator. Differences in the role of LG were found due to female OA, male OA, and female OC's non-significant test of asymmetry and corresponding lower SI resulting in its role as a general joint stabiliser while male OC's asymmetrical activation pattern and high SI resulted in its role as a specific joint stabiliser.

Similar to our reported sex differences, previous studies investigating neuromuscular control reported increased RF activation in healthy, older females compared to males (Bigham et al., *unpublished,* 2014a). While greater RF muscle activation was utilised by male and female OA, it was females with and without OA that

produced less absolute force than males in their respective groups. While greater RF activation in female OA coincided with similar absolute knee extension torques compared to female OC, reduced knee extension torque in male OA may have led to the significantly greater X_{EMG} in RF compared to male OC as a mechanism to generate comparable GRF magnitudes. As both males and females with OA demonstrate similar levels of quadriceps muscle inhibition (Bigham et al., *unpublished,* 2014b), this increased activation appears to be a strategy utilized by females stabilise the joint while producing isometric forces. Increased quadriceps activation has been associated with lower knee extension moments (Schmitt & Rudolph, 2007) decreasing knee joint loading. These results suggest RF plays a greater role in providing stability to the knee joint following the development of OA. This could be in response to altered joint surfaces and quadriceps weakness (Herzog & Longino, 2007). Alternatively, it could be a strategy to increase knee joint stiffness, which would in turn require other muscles to compensate at the hip in order to achieve the target task. Our results suggest male OC are able to maintain a hamstring-dominant strategy to stabilise the knee joint while male OA become quadriceps-dominant as a strategy to increase joint stiffness and counteract high hip extension moments. Along with males and females with OA, healthy females also appear to utilise a quadriceps-dominant activation strategy to maintain joint stability (Bigham et al., *unpublished*, 2014a). Improving eccentric quadriceps strength may therefore improve their ability to stabilise the knee and decelerate the body's centre of mass to protect against high impact loads (Bennell et al., 2013), responses that could improve their joint health.

While the individual muscle roles of the hamstrings were the same in all groups, female OA had significantly greater BF X_{EMG} than female OC in the posterior direction, but produced similar absolute GRF ($p>0.05$). Furthermore, females with OA had the greatest mean normalised BF (51.1%MVIC) activation. Our results demonstrate non-significantly different levels of BF activation compared to male OA (42.5%MVIC). As the knee flexor strength deficit is not significantly different between these groups (Bigham et al., *unpublished,* 2014b), this strategy can be interpreted as a mechanism females adopt in response to joint degeneration to counteract knee adduction moments, which are commonly high in OA populations (Metcalfe et al., 2013; Schmitt & Rudolph, 2007). This strategy may reduce medial joint loads as high knee adduction moments have corresponded with increased medial joint loading during gait (Kumar et al., 2013); therefore, we consider it a healthy stabilisation strategy. The significantly greater activation of BF in female OA compared to female OC in the posterior directions may be an adaptation to cartilage degeneration and/or bony growths in an attempt to increase stability rather than a compensatory mechanism for reduced hamstring strength, as this was not significantly different between groups in our sample. Descriptively, healthy males utilised the highest level of ST activation and had the greatest knee flexor strength compared to all other groups. This suggests healthy females and OA-affected adults have reduced ST function and warrants further investigation into the impact reduced ST function has on joint loading.

Along with increased BF activation in females with OA, significantly greater MG activation was utilized compared to both male OA and female OC suggesting females increase reliance on this muscle's activation to provide joint stability during isometric

tasks following OA development. Peak torque was lower, though not significantly, in healthy and OA-affected females compared to males in their respective groups for both knee flexion and ankle plantar flexion suggesting this strategy, seen only in females with OA, may be a mechanism to compensate for changes in joint integrity which occur with OA. However, while this may increase perceived stability, the long-term influence on joint loading and thus degeneration is unknown. While female OC and male OA had less MG activation during isometric direction-dependent loading, other studies investigating MG's activation pattern during dynamic tasks have reported greater levels of activation in both asymptomatic and moderate OA compared to severe OA (Rutherford et al., 2011). Further investigation into MG activations pattern in older and OA-affected adults is warranted for further understanding of MG's role in joint stabilisation.

As hypothesized, females had more symmetrical activation patterns in most muscles than males in their respective group, and OA participants had more symmetrical activation patterns than OC participants in most muscles within their respective sex. As muscle specificity of the lower limb in OA-affected adults has not been reported, to our knowledge, our results are novel. This reduced muscle specificity is a result of increased activation in multiple directions. We believe more symmetrical activation patterns resulting from these adaptations provide greater contributions to joint stability in OA populations. Since females had less muscle specificity overall than males in their respective groups, their reliance on more symmetrical (generalised) stabilisation strategies may be linked to their increased risk for the development or progression of OA.

High peak knee adduction moment is commonly associated with OA during dynamic tasks (Metcalfe et al., 2013; Schmitt & Rudolph, 2007) however it remains

unclear if it is a risk factor or a result of joint degeneration. Interestingly, our study found a low knee adduction moment in female OA, which is likely a result of their healthy adaptation of increased BF activation in the medial-posterior direction to counteract it. Therefore, we suggest exercise interventions focus on reducing potentially harmful high knee adduction moment by incorporating resisted isometric contractions in the medial-posterior direction to improve BF's role as a specific joint stabiliser.

Limitations of this protocol have been previously reported (Flaxman et al., 2012; Smith et al., 2012; Bigham et al., *unpublished*, 2014a). With respect to this study, we did accept a range of OA severities however our KOOS scores were similar to that of previous studies and therefore we believe our sample is representative of a larger active OA population that is not severely debilitated by their condition. The sample size was relatively small as not all participants were able to successfully match all targets. We suggest future research investigating isometric knee joint stabilisation strategies utilize broader specifications for the level of force produced to provide more insight in neuromuscular strategies of various severities of OA. Also, our representation of normalized EMG may not be a "true" representation of effort level as we accept there are strength deficits in older, healthy females and those with OA (Berth et al., 2002; Bigham et al., *unpublished,* 2014b; Hurley & Scott, 1998).

Our study reports fundamental muscular stabilisation strategies and muscle stabilisation roles in older adults with OA during weight-bearing and how these strategies may influence long-term joint integrity. All groups had similar activation patterns in all muscles, except LG, while utilising different muscular strategies to achieve similar relative GRF. LG in all groups except male OC, RF, VL, VM, and TFL were general

joint stabilisers, BF and MG were specific joint stabilisers, and ST was a moment actuator. We suggest people with OA increase RF X_{EMG} to provide stability by counteracting high hip extension moments and compensating for reduced knee extensor strength. This strategy was also used by older, healthy females compared to age-matched males suggesting this strategy progresses in females with reduced muscle strength resulting from age and OA-associated factors. The increased BF X_{EMG} utilised by female OA is suggested to be a strategy to reduce knee adduction moments may reduce medial joint loading. Our results suggest prophylactic and rehabilitation interventions should focus on the hamstrings, RF, MG, and LG muscles. Improving hamstring and MG function as well as eccentric quadriceps strength should reduce the effort of RF required to resist high hip extension moments while maintaining a stable knee joint. As LG has a more generalized activation pattern, it appears to provide greater levels of stability in male and female OA as well as female OC, increasing its strength in these populations may increase its capacity to provide stability while bearing weight. As our study indicates that muscle activations are a direct function of GRF requirements, intervention strategies to improve neuromuscular control should be conducted over a range of loading directions, not simply using standard flexion/extension protocols. Future research should investigate stabilisation strategies used by people with various levels of OA severity and knee joint function. This will provide even greater insight into altered neuromuscular strategies that could lead to more specific recommendations for interventions aimed at reducing pain, improving knee joint function, and maintaining or slowing down the degeneration of joint cartilage.

Conflicts of Interest

The authors have no conflict of interest.

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ARTICLE 3: A SIMPLE MUSCULOSKELETAL MODEL TO REVEAL QUADRICEPS INHIBITION IN MALES AND FEMALES WITH KNEE OSTEOARTHRITIS

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Key words: quadriceps weakness, quadriceps inhibition, older adults, osteoarthritis, EMG-driven simulation, muscle redundancy

Abstract

Background: Quadriceps weakness and increased muscle activation is commonly reported in healthy, older females and those with knee osteoarthritis (OA). Loss of muscle mass and arthrogenous muscle inhibition contribute to a decrease in muscle strength, and in response it has been suggested that normalised muscle activation increases to compensate. The primary objective of this study was to use a subject-specific musculoskeletal model to determine knee extensor and flexor inhibition in healthy and OA-affected adults over the age of 50. The secondary objective was to evaluate differences between males and females in healthy and OA-affected adults' peak isometric knee extension and flexion torque, as well as agonist muscle force contributions to those torques.

Methods: Peak knee extension and knee flexion torque data from twelve females with OA (64(6) years; 27.0(3.2) kg/m^2), sixteen healthy females (60(5) years; 23.1(2.7) kg/m^2), fourteen males with OA (69(7) years; 25.2(3.8) kg/m^2), and sixteen healthy males (64(8) years; 25.4(2.7) kg/m^2) were collected along with electromyography of eight muscles of the lower limb. Subject-specific knee extension and flexion strength and EMG data were combined with an OpenSim-based modeling framework to determine optimal muscle model parameters. The model was then used to estimate theoretical quadriceps and knee flexor strength deficiencies of males and females with OA compared to healthy controls.

Findings: Relative to the optimal model-produced output, OA participants and healthy females had significantly greater quadriceps inhibition compared to healthy males. Females with OA had the greatest level of quadriceps inhibition. No significant

differences were found between groups in mean absolute or normalised peak knee flexion torque or knee flexor inhibition ($p>0.05$). The relative contributions of the different muscles used to produce the flexor and extensor torque (contribution ratios; $p>0.05$) were also similar between groups.

Interpretation: Knee extensor strength deficits are present in healthy, older females and males and females with OA. Modeling frameworks that do not account for this deficit will over-estimate the force-producing potential of these populations. We suggest subject-specific quadriceps inhibition be accounted for in musculoskeletal models to provide more valid predictions of knee joint loads and thus more physiologically relevant results.

1. Introduction

Quadriceps weakness is commonly reported in people with knee osteoarthritis (OA) (Heiden et al., 2009b; Rudolph et al., 2007; Schmitt & Rudolph, 2007). While this is in part attributed to reduced muscle volume (Berger et al., 2012), it is thought arthrogenous muscle inhibition (AMI) (Hurley et al., 1997) and joint pain (Callaghan et al., 2014) play a role in the reduced voluntary activation of this major muscle group. In healthy, older adults, reduced quadriceps strength was associated with symptomatic OA and increased joint space narrowing in females and similarly, but to a lesser extent in males (Segal et al., 2012). Decreased muscle mass has also been seen alongside the first signs of joint degeneration: reddening and fibrillation of articular cartilage in rabbits (Herzog et al., 2003). Therefore, it appears this inability for the quadriceps muscle to recruit all muscle fibres and the associated loss of muscle mass, strength, and motor control are important factors that may contribute to the development and progression of joint cartilage degeneration (Herzog et al., 2003).

Coinciding with quadriceps inhibition is an increase in quadriceps normalised muscle activation in older adults and those with OA during dynamic (Schmitt & Rudolph, 2007) and isometric tasks (Bigham et al., *unpublished*, 2014a). This increased activation may be a compensatory mechanism for the loss of muscle strength in older adults and those with OA, more specifically females. Negatively, greater and prolonged activation of the quadriceps and hamstrings has been associated with marked joint space narrowing, large osteophytes, and severe sclerosis in a Kellgren-Lawrence grade IV OA group compared to asymptomatic and Kellgren-Lawrence grade II and III during gait

(Rutherford et al., 2013). This suggests that increased activation and the subsequent limb stiffness may alter knee joint loading and could be linked to cartilage degeneration.

A novel weight-bearing target match protocol was used to investigate muscular stabilisation strategies in older adults with and without OA, and reported OA participants produced normalised ground reaction forces (GRF) similar to those of healthy participants (Bigham et al., *unpublished*, 2014b). However, healthy females produced significantly less absolute GRF in all directions compared to healthy males, and females with OA produced absolute GRF that were not significantly different than healthy females. Despite similar absolute GRF, females with OA utilised greater biceps femoris (BF) activation in the posterior direction compared to healthy females, and while producing less absolute GRF than healthy males, healthy females utilised greater rectus femoris (RF) activation in the posterior direction. It was suggested that females with OA increased BF activation to stabilise the joint in the posterior direction despite its role as a specific stabiliser in the medial direction. This suggests BF plays an important role in joint stabilisation in this population; however, the impact this strategy has on joint loading remains unknown. Additionally, both males and females with OA demonstrated increased RF activation compared to healthy adults of the same sex, which may be a protective strategy used to counteract large hip extension moments during posterior-directed force production (Bigham et al., *unpublished*, 2014b). Increased quadriceps strength may enhance their roles as general joint stabilisers and would improve the ability to counteract these moments while maintaining a stable joint, and still allow comparable relative GRF to be produced. Our previous findings demonstrating greater hamstring activation in healthy, older males compared to healthy, older females despite having

greater knee flexion peak torque (Bigham et al., *unpublished*, 2014a), as well as females with OA having greater biceps femoris activation compared to healthy females (Bigham et al., *unpublished*, 2014b), suggests deeper investigation into hamstring strength and inhibition may provide understanding of this strategy used to stabilise the joint and its impact on joint health.

The twitch interpolation technique is commonly used to activate a muscle to its full capacity (Becker et al., 2004; Hurley & Scott, 1998). Previous reports using this technique have found people with OA cannot fully activate their quadriceps during maximum isometric voluntary contraction (Berth et al., 2002; Hurley & Scott, 1998). It has been reported that OA-affected adults have greater voluntary activation deficit, representing quadriceps inhibition, compared to healthy controls (Berth et al., 2002; Pap et al., 2003). Berth et al. (2002) reported Voluntary Activation (VA) of 76.2±13.1%, 90.9±5.5%, for OA-affected adults and healthy controls, respectively, similar to Pap et al.'s (2003) report of VA of 70.8±16.0% in OA-affected adults with stage II chondropathy, 77.2±13.2% in those with more severe cartilage damage (stage IV chondropathy), and 89.3±8.0% in healthy controls. As quadriceps weakness and reduced voluntary activation are seen in older adults compared to younger adults prior to OA development (Mau-Moeller et al., 2013; Stevens et al., 2001), it has been suggested they may be etiological factors contributing to cartilage degeneration (Becker et al., 2004). Furthermore, as prevalence of OA is higher in people over the age of 45 (Statistics Canada, 2012), it would be expected that those with OA would produce a lower peak knee extension torque as a result of reduced levels of quadriceps voluntary activation. In a rehabilitative intervention study, levels of voluntary activation were measured and

compared between an OA-intervention group that participated in two-30 minute exercise sessions each week for five weeks, and an OA-control group that did not participate in prescribed exercise over the five weeks (Hurley & Scott, 1998). Pre-intervention levels were similar between groups (controls: 72%, experimental: 73.5%) while post-intervention levels were significantly different (controls: 76%, experimental: 90%) ($p<0.001$), demonstrating quadriceps function can be improved with physical exercise-based interventions. Implementing these exercises in older adults may be a prophylactic means of improving knee-joint health and reducing the risk of OA development.

As quadriceps play an important role in providing general stability to the joint (Bigham et al., *unpublished,* 2014b), it is vital to understand the level of activation deficit in various populations. This knowledge will enhance the success of intervention programs in "at risk" populations as well as those already affected with OA, as increases in quadriceps function are expected to improve their ability to stabilise the knee joint.

Our proposed modeling framework is a novel method to estimate strength deficits in older and OA-affected males and females eliminating the reliance on the more invasive method of the super-imposed twitch technique. This method can be used to provide reliable estimations of subject-specific strength deficits and adjusted maximum isometric muscle forces to account for physiologically relevant changes that occur in various populations. This will improve the validity of model simulations of muscle forces and consequently, the prediction of joint loads from musculoskeletal simulations.

Therefore, we propose the use of this novel subject-specific model to determine the quadriceps and knee flexor level of voluntary activation in older males and females with and without OA through a ratio of a scaled voluntary *experimental* peak torque

production versus the model output *ideal* peak torque production. Between-group differences in peak knee extension and flexion torque (Nm) and normalised knee extension and flexion torque (Nm/kg) will also be investigated. We hypothesise that healthy females and all OA participants will have greater quadriceps inhibition than healthy males and that females with OA will have the greatest hamstring inhibition. Accordingly, females with OA will produce the least amount of knee extension torque, even when normalised to body mass. Absolute peak knee flexion torque will be lower in females but have no significant difference between OA-affected and healthy control groups (Rutherford et al., 2011).

2. Methods

2.1 Participants

Participants' torque data for this study was collected as part of a larger study investigating muscular stabilisation strategies and individual muscle roles in providing stability to the knee joint (Bigham et al., *unpublished*, 2014b). Peak knee extension and knee flexion torque data from twelve females with OA (FOA) (64(6) years; 27.0(3.2) kg/m^2), sixteen healthy older females (FOC) (60(5) years; 23.1(2.7) kg/m^2), fourteen males with OA (MOA) (69(7) years; 25.2(3.8) kg/m^2), and sixteen healthy older males (MOC) (64(8) years;) 25.4(2.7) kg/m^2 was collected (n=58). Inclusion criteria for all participants included: over the age of fifty and physically active at least two days a week. MOA and FOA participants were previously diagnosed with radiographic knee OA. Exclusion criteria for all participants included: a significant lower limb injury (i.e. ligament rupture), a lower limb fracture, a lower extremity motor nerve lesion,

corticosteroid injection, and/or the presence of a knee joint effusion within six months prior to participation; diabetes; BMI $\geq$35kg/m^2; and any other physical or neurological impairment that could affect the results of this study. All participants gave written consent and the University of Ottawa Research Ethics Board approved this study.

2.2 Knee Osteoarthritis and injury Outcome Score (KOOS)

All participants filled out the KOOS, which rates knee-related symptoms, pain, function/daily living, function/sports and recreation, and quality of life, on a 5-point Likert scale (Roos et al., 1998). Scores were converted to a scale of 0-100, 0 representing poor knee-joint health, 100 representing the best knee-joint health. KOOS has been proven to be a valid and reliable tool for measuring knee-joint health in older populations with knee OA (Roos & Lohmander, 2003).

2.3 Electromyography (EMG)

Eight muscles of the lower limb were fitted with fixed bipolar surface electrodes (SP-E04, DE 2.1, Delsys Inc., MA) 10mm in length, 1mm wide, and spaced 10mm apart: rectus femoris (RF), vastus lateralis (VL), vastus medialis (VM), biceps femoris (BF), semitendinosus (ST), lateral gastrocnemius (LG), medial gastrocnemius (MG), and tensor fascia latae (TFL) according to SENIAM guidelines (Hermens et al., 2000). EMG was captured at 1000Hz, amplified by a gain of 1000, band-pass filtered at 20-450Hz using a 16-bit A/D conversion board (NI PCI 6229, National Instruments Corp., Austin, TX), and recorded by a custom-made *Matlab* application (2007b, Mathworks, Natick, MA).

2.4 Isometric peak torque and MVIC

Isometric peak torque production of knee extension and knee flexion was recorded using an isokinetic dynamometer (850-000, Biodex, Shirley, NY). Participants were seated with

their hip and knee joints at approximately 30° flexion. Participants were asked to ramp up their force from 0-100% and hold the maximum for approximately three seconds. Three repetitions of each movement were completed. Analog signals of torque, position, and velocity were exported through the remote access port of the isokinetic dynamometer in real time at 1000Hz to an A/D conversion board (NI PCI 366229, National Instrument Corp., Austin, TX). They were collected along with EMG to obtain MVIC data using a custom-made *Labview* application (v.8.20, National Instruments Corp., Austin, TX).

Data Analysis: EMG and torque data from MVIC were filtered with a 4th order Butterworth dual low-pass filter (6Hz) in a custom-made *Labview* application (v.8.20, National Instruments Corp., Austin, TX). EMG also had bias removed, and then was full wave rectified in that application. Peak torque had bias removed and then fifty data points (50ms) before and after peak torque were averaged in a custom-made *Matlab* application (2010b, Mathworks, Natick, MA). This determined the peak torque value and the cell index it occurred at for both knee extension and knee flexion. The cell indices were used to call the corresponding filtered muscle activation of each of the eight muscles. Fifty data points (50ms) before and after the indexed cells were averaged and normalised to the maximum EMG of each muscle to represent the level of each muscle's normalised EMG at peak torque.

2.5 Model description

OpenSim Gait-2354 model (Thelen et al., 2013) was used to extract moment arms of the muscles. These moment arms around the hip, knee, and ankle sagittal plane rotations were computed by setting the hip, knee, and ankle joint angles to 30° flexion,

30° flexion, and 10° plantar flexion, respectively. Within a mathematical framework using optimization, maximum isometric force parameter $F_0^{\max}$ of the muscles was tuned so that the error between the simulation and the measured torques was minimised. Lower and upper bounds for the scale parameters were set to 0.2 and 6.0, respectively. Initial values for the scales were set to so that $F_0^{\max}$ corresponded to those of Delp et al. (1990). This simulation was performed in a *Matlab* application (2010b, Mathworks, Natick, MA) where a combination of a genetic algorithm (GA), sequential quadratic programming (SQP), and direct search (DS) was used to assure convergence; see (Shourijeh and McPhee, 2014a or 2014b for more details on the convergence aspects). For greater reliability, the mean of 10 repeated runs was recognized as optimal scale parameters. Figure 13 shows the schematic of the simulation workflow used in this study. The muscle model applied here was an ideal type, i.e., each muscle force is calculated as normalised EMG multiplied by the scaled$F_0^{\max}$. Then the model joint torque was computed as:

$$T^m = \sum_{i=1}^{7} s_i * F_{0,i}^{\max} * r_i * a_i$$

where a, r, and s designate the normalised EMG, moment arm, and scale parameter of the muscle; i shows the muscle index, which is from 1 to 7.

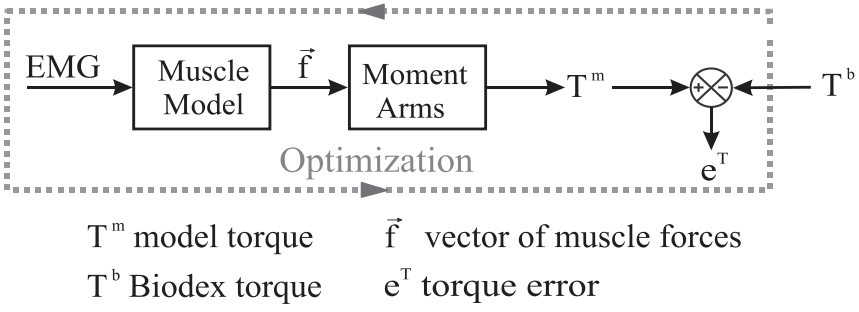

Figure 13: Schematic of EMG-driven strength tuning framework.

Optimal parameters were used afterwards to compute the *ideal* torque, which represented the muscles' full capacity of activation. The *ideal* joint torque had all agonist muscles set at 100% of their potential muscle force with antagonist muscles producing no opposing force. Using the torque contribution of each agonist muscle, ratios for RF, VL, and VM's contribution to peak knee extensor torque, and BF, ST, LG, and MG's contribution to peak knee flexor torque were calculated, which sum to 1.0. A strength ratio α_s representing the level of voluntary activation defined as:

$$a_i = T^b / T^I,$$

where T^b is the *Experimental* (Biodex) peak torque and T^I is the *Ideal* peak torque, was calculated for each participant to determine quadriceps and knee flexor strength deficiencies (lower value represents greater level of activation deficiency).

The torque contribution of each agonist muscle is calculated as follows. Ratios for RF, VL, and VM's contribution to peak knee extensor torque:

$$C_j^E = \frac{s_j F_{0,j}^{\max} r_j a_j}{\sum_{j=1}^{3} s_j F_{0,j}^{\max} r_j a_j}$$

Ratios for BF, ST, LG, and MG's contribution to peak knee flexor torque:

$$C_k^F = \frac{s_k F_{0,k}^{\max} r_k a_k}{\sum_{k=1}^{4} s_k F_{0,k}^{\max} r_k a_k}.$$

C is for contribution; indices $j \in \{1,2,3\}$ and $k \in \{1,2,3,4\}$ refer to extensor and flexor muscles, respectively; and superscripts E and F represent Extensor and Flexor, respectively. Note that the contributions for each group will sum to 1.0.

2.6 Statistical Analysis

One-way analysis of variance (ANOVA) tests were used to determine between-group differences in KOOS subscale and total scores, absolute (Nm) and normalised (Nm/kg)

peak knee extension and flexion torque (Nm), and knee extensor and flexor torque level of voluntary activation. A MANOVA was used to determine between-group differences in quadriceps muscle contribution ratios to peak knee extension, as well as in BF, ST, LG, and MG contribution ratios to peak knee flexion torque. An adjusted alpha level of 0.017 was used for quadriceps contribution as three quadriceps muscles were tested, and an adjusted alpha level of 0.0125 was used for knee flexor contributions, as there were four knee flexors tested. In cases of significance a post-hoc test was applied to locate the between-group differences. The alpha level was set at 0.05 for all tests, unless otherwise stated. All statistical analyses were completed in SPSS (v.21.0, IBM, Chicago, IL).

3. Results

KOOS: Mean ± standard deviation KOOS total scores were: 96.5± 4.1 for healthy males, 94.9± 5.5 for healthy females, 69.6± 15.1 for males with OA, and 63.2± 12.4 for females with OA. These results are similar to previous findings (Kumar et al., 2013), with OA participants having significantly lower total and subscale scores than healthy controls ($p<0.01$).

Isokinetic Dynamometer: Absolute peak knee extension torque (Nm) produced on the Biodex was significantly less in females with and without OA, and males with OA, compared to healthy males ($p<0.03$) (Table 4). However, when absolute peak knee extension torque was normalised to body mass, only females with OA had significantly less peak torque production (Nm/kg) than healthy males ($p=0.005$) (Table 4). Mean absolute and normalised knee flexion torques were not significantly different between groups ($p>0.05$).

Table 4: Mean ± standard deviation absolute and normalised peak knee extension and flexion torques for females and males with OA (FOA, MOA), and healthy controls (FOC, MOC). (KE represents knee extension; KF represents knee flexion) Asterisks (*) represent significant difference between MOC and all other groups ($p<0.05$).

	FOA	MOA	FOC	MOC
Absolute KE Torque (Nm) mean±SD	80.5±22.5	93.1±24.3	84.2±17.8	118.8±27.3*
Normalised KE Torque (Nm/kg) mean±SD	1.09±0.26	1.27±0.37	1.41±0.28	1.53±0.36
Absolute KF Torque (Nm) mean±SD	53.2±17.0	60.5±20.4	50.2±12.5	62.7±16.2
Normalised KF Torque (Nm/kg) mean±SD	0.72±0.20	0.83±0.27	0.84±0.16	0.80±0.19

Model results: Based on the optimal model-derived force production capability of the subjects, the mean level voluntary activation of the quadriceps was significantly lower in OA males, OA females, and healthy females compared to healthy males ($p=0.023,0.007, 0.001$, respectively) (Fig. 14). This represented greater quadriceps strength deficiencies in these groups. Mean ± standard deviation quadriceps muscle contribution ratios were not significantly different between groups ($p>0.05$); however, standard deviations were high in all groups (Table 5), suggesting this variable is subject-specific.

Ratios of mean ± standard deviation knee flexion level of voluntary activation were not significantly different between groups ($p>0.05$) (Fig. 15). These low values are in part due to not including the contribution of the semimembranosus, as well as the gastrocnemius muscles never activating 100% during maximal knee flexion effort in experimental settings. We therefore suggest these values are not representative of hamstrings activation deficits; however, the non-significant differences between groups support the notion that the level of hamstring voluntary activation is similar in older adults irrespective of sex and the presence of OA. Hamstring and gastrocnemius muscle contributions to the maximum torque were not significantly different between groups ($p>0.05$) and had relatively low standard deviations (Table 5).

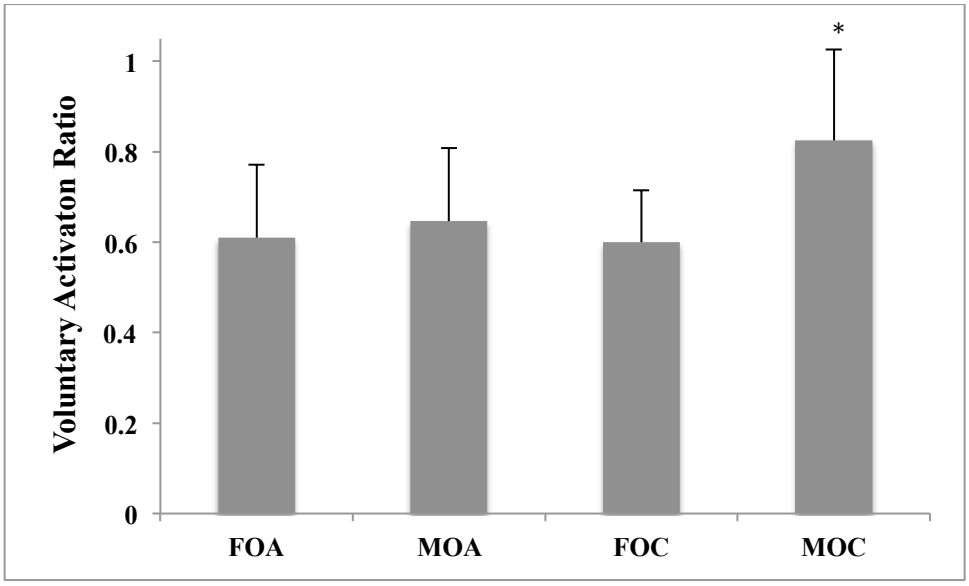

Figure 14: Mean voluntary activation ratios, representing level of quadriceps function, in females and males with OA (FOA, MOA) and healthy controls (FOC, MOC). Error bars represent standard deviation. Asterisks (*) represents significant difference between MOC and all other groups ($p<0.05$).

Table 5: Mean ± standard deviation muscle ratio of contribution of agonist muscles towards maximum torque production of knee extension and knee flexion in females and males with OA (FOA, MOA) and healthy controls (FOC, MOC). The sum of all agonist muscles' contribution equals 1.0.

Movement/Muscle	FOA	MOA	FOC	MOC
Knee Extension				
RF	0.20±0.15	0.21±0.19	0.16±0.08	0.23±0.14
VL	0.55±0.21	0.55±0.25	0.54±0.15	0.50±0.14
VM	0.25±0.17	0.24±0.16	0.30±0.14	0.27±0.11
Knee Flexion				
BF	0.48±0.11	0.54±0.15	0.53±0.14	0.44±0.12
ST	0.25±0.09	0.18±0.13	0.23±0.12	0.26±0.09
LG	0.09±0.05	0.12±0.07	0.08±0.04	0.09±0.05
MG	0.18±0.12	0.15±0.06	0.15±0.08	0.21±0.11

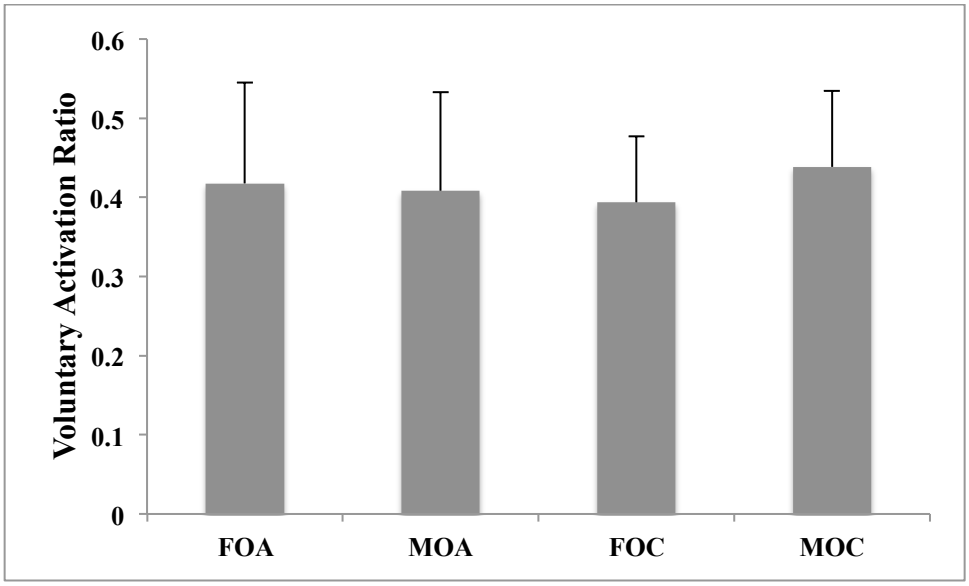

Figure 15: Mean voluntary activation ratios, representing level of knee flexors function, in females and males with OA (FOA, MOA) and healthy controls (FOC, MOC). Error bars represent standard deviation. **Note: this value is not representative of the level of hamstrings inhibition due to generalised settings of the gastrocnemius muscles activated 100% and the exclusion of the semimembranosus' contribution during maximum knee flexion.*

4. Discussion

The main finding of this study was that males and females with OA, along with healthy females, have greater quadriceps inhibition represented by lower levels of voluntary activation of the quadriceps during maximum torque production whereas there were no significant between-group differences found in hamstring inhibition. Interestingly, muscle contribution ratios to produce maximum knee extension and knee

flexion torque were not significantly different between groups. Our mean absolute peak knee extension and flexion torque were comparable to previous findings (Newman et al., 2003, Rutherford et al., 2011). As expected, males and females with OA produced less absolute (Nm) knee extension torque compared to healthy males. Females with OA had the lowest normalised knee extension torque. Our study, along with others (Conroy et al., 2012), found similar absolute quadriceps strength (Nm) between radiographic OA and healthy control females. Therefore, we believe our results to be representative of older male and female populations with and without OA.

Interestingly, while peak knee extension torque was significantly larger in older male controls compared to all other groups and no significant between-group differences were found in peak knee flexion torque, all four groups utilised non-significantly different muscle contribution ratios and similar levels of normalised EMG activation to contribute to those peak torques. These results suggest relative activation strategies to produce knee flexion force at maximum effort are not significantly impacted by changes in joint integrity caused by OA.

Regarding activation deficits, our results agree with others in that males with OA have greater quadriceps inhibition than males without OA (Becker et al., 2004). Interestingly, females with and without OA had similar levels of quadriceps inhibition, both significantly less than healthy males. Interestingly, mean normalised EMG during peak torque was not significantly different between quadriceps muscles or between groups and ranged from 70-77%MVIC. This level was lower than expected and suggests all agonist muscles activate to a similar relative level to achieve maximum torque production. Mean normalised EMG of BF, ST, LG, and MG during peak torque were not

significantly different between groups. Mean hamstring EMG was 66-75% MVIC and mean gastrocnemius EMG was lower and ranged 52-65% MVIC between groups. This suggests that when normalised levels of agonist muscles are similar, it is the optimal scenario to produce the greatest level of torque. Interestingly, VL and BF's activation contributed to approximately half the maximum knee extension and knee flexion torque, respectively, suggesting they play a greater role in producing these torques. MG and LG utilised lower levels of activation suggesting they play a secondary role in producing maximum knee flexion torque. As our *ideal* knee flexion torque set MG and LG at 100% active, this, along with not including semimembranosus' contribution, led to our low values for knee flexor voluntary activation.

While we did not have all the OA participants' level of severity, our OA participants had significantly lower KOOS scores than healthy controls ($p<0.01$). Hurley et al. (1997) suggested that degenerative changes to knee joint structures alter sensorimotor function, diminishing alpha motoneuron output, causing AMI, however it remains unclear if increased levels of cartilage degeneration directly effects the level of AMI. Our KOOS scores not only confirmed our OA patients had reduced knee-health, but the subscales informed us of the perceived pain levels our participants dealt with. While pain was rarely reported during the protocol, OA participants had significantly lower pain-subscale scores than the controls ($p<0.05$).

Quadriceps inhibition has been previously reported in people with OA (Becker et al., 2004; Hurley & Scott, 1998) supporting suggestions that quadriceps weakness is a result of more complex factors than muscle atrophy alone in older populations. Our model's output of *Experimental/Ideal* torque suggests males with OA have significantly lower

levels of voluntary activation of the quadriceps than healthy males. This has previously been determined using the super imposed twitch technique (Becker et al., 2004). Our finding of reduced voluntary quadriceps activation in OA participants corresponds with greater normalised RF activation during isometric direction-dependent loading (Bigham et al., *unpublished*, 2014b) suggesting this increased activation is a compensatory mechanism to decreased strength capacity. Furthermore, females with and without OA both used greater mean RF activation to stabilise the knee, yet, as a result of their increased quadriceps activation deficit, have greater quadriceps weakness and produce less GRF during isometric stabilisation tasks than healthy male controls (Bigham et al., *unpublished*, 2014a,b). As quadriceps are classified as general joint stabilisers due to their symmetrical activation patterns (Bigham et al., *unpublished*, 2014b), RF's increased activation suggests it is an adaptation to compensate for muscle weakness as a means to provide sufficient stability to the joint (Bigham et al., *unpublished*, 2014a,b). This may be an effective activation strategy to provide stability; however, its long-term effect on joint loading has yet to be investigated.

Fortunately, increasing quadriceps strength will improve its function and this is expected to improve quadriceps muscle activation. As this increased strength should also enhance the ability of the muscles absorb the loads and maintain stability during weight-bearing rather than the load being absorbed by damaged bone/cartilage further progressing joint degeneration. Quadriceps function can also be enhanced with adequate instruction, feedback, and allowing several attempts to reach maximum contraction which are techniques that have been shown to decrease activation failure (Hurley & Newham, 1993, Lewek et al., 2004). Exercise interventions incorporating knee flexion and

extension strengthening exercises increased strength and function, and reduced levels of pain and disability in OA patients (Hurley & Scott, 1998). As strength deficits appear to have a negative impact on joint integrity, determining individuals' strength deficit may lead to improved focus for rehabilitation programs. Therefore, it is suggested that by incorporating functional exercises and adequate instruction and feedback, quadriceps function and agonist-antagonist muscle balance is expected to improve.

Interestingly, while no significant differences were found between groups in knee flexion torque production, females with OA used significantly greater normalised BF activation than healthy females to stabilise the joint during posterior-directed force production (Bigham et al., *unpublished*, 2014b). Interestingly, despite having greater BF activation in these directions, GRF produced remained similar between these groups suggesting BF must activate more to maintain stability in females with OA in these directions. These altered muscle contributions to joint stability while bearing weight may be adaptations to changes in joint structures, however, they may negatively impact joint loading further progressing OA. Further research on the impact these altered activation strategies have on joint loading would provide valuable information progressing the success of physical rehabilitation programs for those with OA. A strengthening program focused on functional tasks requiring flexors and extensors to coordinate contractions to reduce imbalanced joint loading may increase joint stability and protect joint structures from further degeneration.

5. Conclusion

This study presents a novel method for estimating quadriceps strength deficiencies during maximum effort. Our model produced subject-specific estimations of voluntary activation levels with minimal error allowing us to quantify quadriceps inhibition as the deficit in level of voluntary activation achieved compared to the quadriceps' capacity to produce maximum knee extensor torque. Healthy females had similar levels of quadriceps inhibition than those with OA suggesting this may be an etiological factor that increases risk of OA development in this sex. Improving quadriceps strength and function should be a priority for prophylactic interventions, especially in healthy females. Additionally, despite no significant differences in peak knee flexor torque or normalised muscle activations to achieve that peak torque between females with and without OA, females with OA used increased BF activation as a strategy to increase joint stability during isometric direction-dependent loading. Therefore, further investigation into hamstrings function in older females with and without OA is warranted. Also, as our results support the notion that quadriceps inhibition is present in older males and females with and without OA, we suggest generic musculoskeletal models should make necessary adjustments for this valid variable to improve the reliability of their model output predictions.

Conflict of interest statement

The authors report no conflict of interest.

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General Discussion and Conclusions

As discussed, neuromuscular adaptations, such as increased EMG activity and reduced knee joint function, are associated with aging and OA development. As females have a greater risk of developing OA, it is important to understand the sex differences in these adaptations in healthy and OA populations. Using our novel target matching protocol, we investigated these adaptations. Therefore, the purpose of this thesis was to answer the research question: What adaptations in neuromuscular control are associated with aging and OA in males and females? The first paper investigated sex differences in older, healthy adults to first establish strategies of isometric joint stabilisation and aimed to link them to strategies that may negatively effect joint loading in females leading to their increased risk of OA development. Mean ensemble activation levels as well as mean activation levels at each target direction were used to determine neuromuscular adaptations, while SI, mean resultant direction, and a measure of asymmetry determined activation patterns and consequently individual muscle roles as they contribute to knee joint stability. Maximum joint torques of four lower limb movements were also collected during MVIC and compared between sexes to determine absolute and normalised strength differences. Low SEMs suggest activation profiles of all eight muscles were reliable in all groups suggesting our results are representative of a non-random sex-based neuromuscular control strategy. Results found older, healthy males and females utilise similar muscle stabilisation patterns in all investigated muscles except LG, which exhibits a more specific pattern in males, while producing similar relative GRF in the lateral, anterior, and medial directions. Females had weaker knee extensors, knee flexors, ankle plantar flexors, and hip abductors than males and produced less absolute GRF in all

directions. Despite the similar activation patterns, neuromuscular strategies differed as females utilised greater RF X_{EMG} and had reduced specificity in most muscles resulting in more general stabilisation patterns. Males utilised greater hamstring X_{EMG}, specifically an increase in BF activation in the medial-posterior direction and this may be a mechanism to counteract the high knee adduction moment to reduce medial joint loading and increase knee joint stability. Large hip extension and adduction moments were used during successful target matches in the posterior and medial directions, respectively, suggesting they act as actuators to produce isometric GRF in various directions.

Medial and posterior GRF were nearly half that produced by younger healthy adults (Flaxman et al., 2014) suggesting the ability to produce force in these directions is reduced with age. While producing less force in the medial and posterior directions, older adults also had greater normalised hamstring activation compared to other directions indicating increased muscular effort is a compensation mechanism for reduced strength and loss of neuromuscular control commonly reported in older adults (Madhavan et al., 2009). Interestingly, despite males producing significantly greater peak knee flexion torque than females, they utilised greater normalised hamstring activity to produce these forces. This may be a strategy to reduce imbalanced loading at the knee joint during medially directed force production as a mechanism to increase stability. These results suggest females are insufficiently activating their hamstrings to maintain stability and therefore are adapting their muscular activation strategy to maintain joint position and produce isometric forces. If so, implementing prophylactic interventions focused on muscles with altered strategies to stabilise the joint (RF, BF, and LG muscles) could have beneficial effects. Furthermore, improving hamstring function and quadriceps-hamstrings

muscle coordination to reduce harmful joint loading are strategies expected to improve knee stability while bearing weight.

Our second aim was to include males and females with OA to investigate isometric stabilisation strategies and identify individual muscle roles to providing joint stability that were associated with people with structural changes in the knee joint. Mean ensemble activation levels and mean activation levels at each direction were used again to determine neuromuscular adaptations between sexes and groups, while SI and a measure of asymmetry determined activation patterns. Results of statistical testing reported muscle activation patterns (asymmetry, SI, ϕ) were similar between groups in all muscles except LG, which had significantly greater SI in healthy males compared to healthy females, as well as males and females with OA. Female OA had lower BF and LG activation specificity (SI) than the other groups as a result of more generalised activation of these muscles at other target directions. We suggest this increased muscular activation is required to compensate for muscle weakness and changes in joint surfaces to allow this group to produce relative GRF similar to the other groups. Additionally, while producing similar normalised GRF, males and females with OA utilised significantly greater RF X_{EMG} than healthy controls of the same sex. Interestingly, females with OA had the greatest BF X_{EMG} while male OC utilised the greatest ST X_{EMG}. The OA-affected participants and healthy females did not achieve the increased ST activation, despite having reduced muscle strength. As hamstring activation plays a vital role in joint stabilisation in reducing anterior shear force (Beynnon et al., 1997), this finding suggests the inability to sufficiently active ST when producing forces and stabilising the joint may

lead to increased shear loading. This may negatively impact joint integrity and increase prevalence and progression of OA in older adults, to a greater extent in females.

Increased normalised muscle activation also resulted in reduced muscle specificity in males and females with OA and healthy females, resulting in muscles acting in more symmetrical activation patterns. This suggests these are adaptations to maintain joint stability while performing the same force-control task. Our results suggest prophylactic and rehabilitation interventions should focus on the hamstring, RF, MG, and LG muscles. Improving hamstring function as well as eccentric quadriceps strength should reduce the effort of RF required to resist high hip extension moments while maintaining a stable knee-joint. Additionally, as LG appears to provide greater levels of stability in OA participants and healthy older females, increasing its strength in these populations may increase its capacity to provide stability while weight-bearing.

The third aim of this thesis was to investigate quadriceps and knee flexor strength deficits, as well as knee flexor and extensor peak torque differences between males and females with and without OA. Data from the MVIC collection was used to determine peak torque and corresponding normalised EMG to investigate muscle contribution ratios to peak knee extensor and flexor torque respectively. A model was used to estimate subject-specific quadriceps and knee-flexor strength deficiencies by creating a ratio between the agonist muscle contributions to experimental peak knee extensor torque (from the Biodex), versus the model predicted peak knee extensor torque. The model had all agonists activated 100% and antagonists not activated. Our statistical analyses reported, as expected, that male with OA, and females with and without OA had significantly lower quadriceps voluntary activation ratios, representing greater quadriceps

strength deficits, during peak knee extensor torque production compared to healthy males. Females with and without OA, as well as males with OA, had significantly less absolute peak knee extension torque during MVIC collection, however, only females with OA had significantly less peak knee extensor torque when normalised to BM.

We suggest quadriceps inhibition is an etiological factor that increases risk of OA development as it was seen in healthy female controls and those with OA. Improving quadriceps strength and function should be a priority for prophylactic interventions, especially in older females. Appropriate rehabilitation programs for those with OA are required to train their lower limb muscles to coordinate in a manner that optimizes joint loading conditions, which is expected to slow down or stop the progression of OA. Additionally, despite no significant differences in peak knee flexor torque or normalised muscle activations to achieve that peak torque, females with OA used increased BF activation as a strategy to increase joint stability during isometric direction-dependent loading. Therefore, further investigation into hamstrings function in older females with and without OA is warranted.

Our results support the notion that quadriceps inhibition is present in older males and females with and without OA and that the generic but widely used musculoskeletal model used was not robust in predicting the voluntary isometric torque that our populations could produce. This suggests that musculoskeletal models should make necessary adjustments for populations they are going to be used to represent in order to produce more valid predictions of physiological events.

In conclusion, our novel weight-bearing target match protocol has provided valuable insight into sex differences of isometric stabilisation strategies in older healthy

adults and those with OA. These findings of similar muscular activation patterns, while using different neuromuscular control strategies between males and females with and without OA, suggests most muscle roles in providing joint stabilisation are maintained with the presence of OA, and furthermore that the altered strategies used by females and those with OA may be a compensatory mechanism for muscle weakness and quadriceps dysfunction. We suggest increased risk of OA development in females is partly a result of their lower muscle mass and increased quadriceps inhibition, which is seen to a greater extent in females with osteoarthritic changes in knee joint structures. Therefore, prophylactic interventions should focus on RF, hamstring, and gastrocnemius muscles to improve knee joint stability. As activation strategies differ in OA-affected and "at risk" older females populations compared to healthy males that are less likely to develop OA, improving strength and function is expected to slow down the progression of joint degeneration. Further research investigating the changes these altered strategies have on joint contact forces as well as the long-term impact on joint health that results from improved muscle function in older, healthy females, and OA-affected adults is warranted.

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Appendix A: KOOS (Knee Osteoarthritis and injury Outcome Score)

KOOS KNEE SURVEY

Today's date: _____/_____/_____ Date of birth: _____/_____/_____

Name: _____

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the **last week**.

S1. Do you have swelling in your knee?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S3. Does your knee catch or hang up when moving?

Never	Rarely	Sometimes	Often	Always
☐	☐	☐	☐	☐

S4. Can you straighten your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

S5. Can you bend your knee fully?

Always	Often	Sometimes	Rarely	Never
☐	☐	☐	☐	☐

Stiffness
The following questions concern the amount of joint stiffness you have experienced during the **last week** in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day**?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Pain

P1. How often do you experience knee pain?

Never	Monthly	Weekly	Daily	Always
☐	☐	☐	☐	☐

What amount of knee pain have you experienced the **last week** during the following activities?

P2. Twisting/pivoting on your knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P3. Straightening knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P4. Bending knee fully

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P5. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P6. Going up or down stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P7. At night while in bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P8. Sitting or lying

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

P9. Standing upright

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A1. Descending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A2. Ascending stairs

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A3. Rising from sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A4. Standing

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A5. Bending to floor/pick up an object

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A6. Walking on flat surface

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A7. Getting in/out of car

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A8. Going shopping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A9. Putting on socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A10. Rising from bed

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A11. Taking off socks/stockings

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A12. Lying in bed (turning over, maintaining knee position)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A13. Getting in/out of bath

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A14. Sitting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A15. Getting on/off toilet

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

For each of the following activities please indicate the degree of difficulty you have experienced in the **last week** due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

A17. Light domestic duties (cooking, dusting, etc)

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP2. Running

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP3. Jumping

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP4. Twisting/pivoting on your injured knee

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

SP5. Kneeling

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Quality of Life

Q1. How often are you aware of your knee problem?

Never	Monthly	Weekly	Daily	Constantly
☐	☐	☐	☐	☐

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

Not at all	Mildly	Moderately	Severely	Totally
☐	☐	☐	☐	☐

Q3. How much are you troubled with lack of confidence in your knee?

Not at all	Mildly	Moderately	Severely	Extremely
☐	☐	☐	☐	☐

Q4. In general, how much difficulty do you have with your knee?

None	Mild	Moderate	Severe	Extreme
☐	☐	☐	☐	☐

Thank you very much for completing all the questions in this questionnaire.

Appendix B: University of Ottawa Modified Plug-in Gait Marker Set

Figure 16: Visual representation of the University of Ottawa's marker placement set.

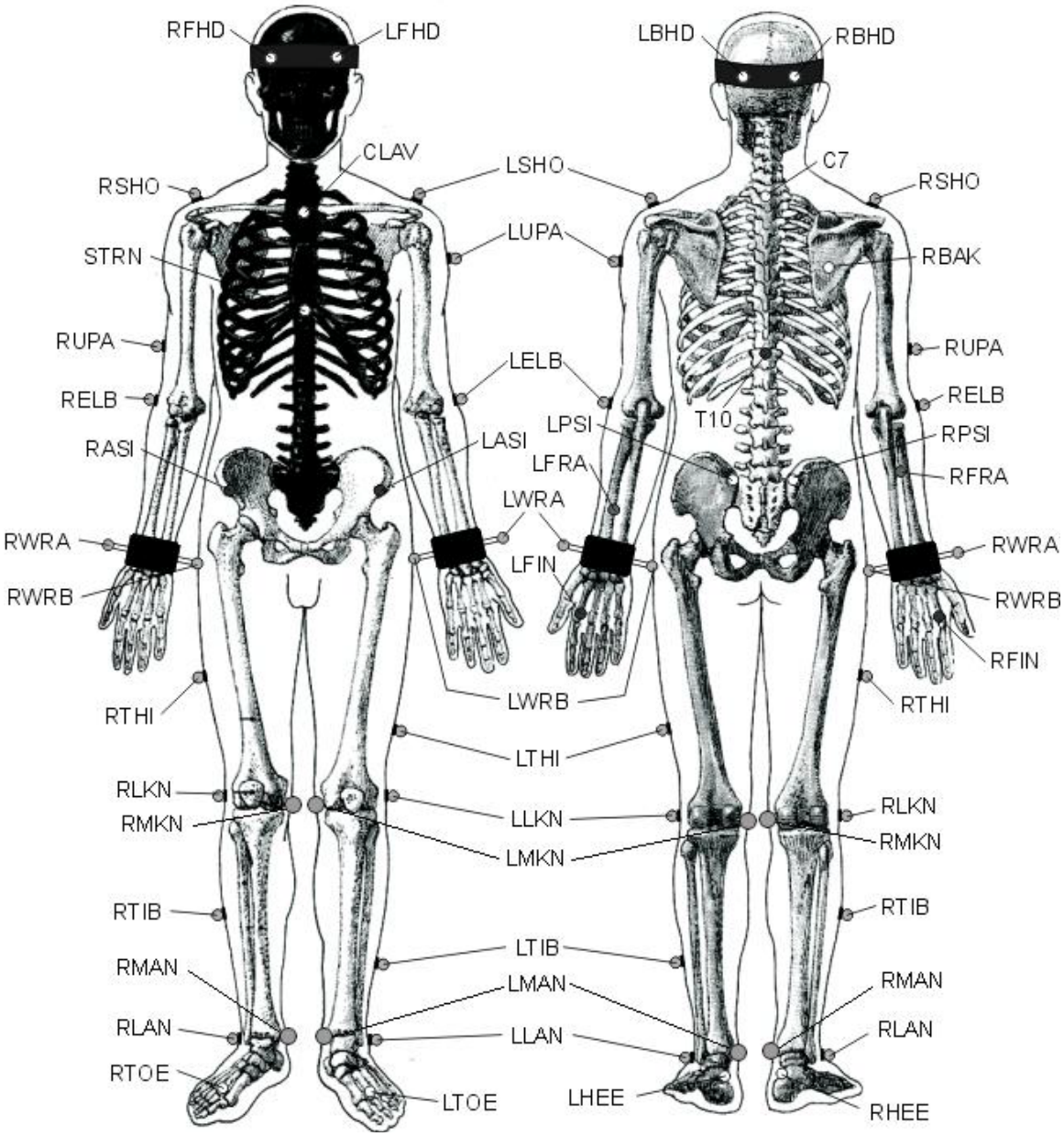

Table 6: Markers and their respective acronym descriptions that were used to record kinematics during this study. Each description corresponds to the location of marker placement on the participant. Acronyms beginning with an "L" or "R" correspond to the left and right sides, respectively.

Head	
LFHD & RFHD	Left temple
LBHD & RBHD	Left back of head
Torso	
C7	7th cervical vertebrae
T10	10th thoracic vertebrae
CLAV	Jugular notch
STRN	Xiphoid process
RBAK	Middle of right scapula
Arms	
LSHO & RSHO	Acromio-clavicular joint
LUPA & RUPA	Upper arm
LELB & RELB	Lateral epicondyle
LFRA & RFRA	Forearm
LWRA & RWRA	Wrist bar thumb side
LWRB & RWRB	Wrist bar pinkie side
LFIN & RFIN	Dorsum of the hand head of 2nd metacarpal
Pelvis	
LASI & RASI	Anterior superior iliac crest
LPSI & RPSI	Posterior superior iliac spine
Legs	
LTHI & RTHI	Lateral thigh
LMKN & RMKN	Medial epicondyle of the knee
LKNE & RKNE	Lateral epicondyle of the knee
LTIB & RTIB	Lateral shank
LANK & RANK	Lateral malleolus
LMAN & RMAN	Medial malleolus
Feet	
LTOE & RTOE	2nd metatarsal head of foot
LHEE & RHEE	Posterior calcaneus

Appendix C: Reported OA Severity Levels

Table 7: Reported severity of male and female OA participants.

Reported OA Severity	MOA	FOA
Mild	3	5
Mild-Moderate	2	1
Moderate	1	3
Severe	2	1

Appendix D: Report of SPSS Statistics

Note: Asterisks (*) represent significant variables. SD represents standard deviation.

Article 1

Table 8: Independent t-test results of group differences in peak absolute and normalised knee extension, knee flexion, ankle plantar flexion, and hip abduction torques in older males and females.

Movement	Sex	Mean	SD	*p* Value
Hip Abduction (ABD)	Male	66.05	18.56	0.016*
	Female	51.28	14.07	
Knee Extension (EXT)	Male	116.27	27.91	<0.001*
	Female	81.67	20.11	
Knee Flexion (FLX)	Male	65.70	17.41	0.003*
	Female	49.26	12.66	
Ankle Plantar Flexion (PLA)	Male	75.20	21.01	0.002*
	Female	53.30	18.53	
ABD_norm	Male	0.84	0.24	0.507
	Female	0.77	0.36	
EXT_norm	Male	1.49	0.37	0.339
	Female	1.38	0.31	
FLX_norm	Male	0.83	0.21	0.937
	Female	0.83	0.16	
PLA_norm	Male	0.95	0.27	0.714
	Female	0.92	0.35	

Table 9: A) MANOVA (Wilk's Lamda) results for absolute and normalised GRF in older males and females, B) between-group effects of absolute and normalised GRF in older males and females. (adjusted alpha=0.025)

A.

	Main Effect of Group		Interaction	
	F	*p* Value	F	*p* Value
GRF Absolute	138.643	<0.001**	5.682	<0.001**
GRF Lateral	0.115	0.892		
GRF Anterior	2.483	0.099		
GRF Medial	1.533	0.231		
GRF Posterior	3.656	0.037		

B.

			Mean	SD	*p* Value
GRF Absolute		**x**			<0.001*
		y			<0.001*
GRF Lateral	**Female**	**x**	0.5478	0.11897	0.780
		y	0.0254	0.01699	0.661
	Male	**x**	0.5374	0.10274	
		y	0.0214	0.03367	
GRF Anterior	**Female**	**x**	0.0366	0.02547	0.664
		y	-0.4381	0.11652	0.031
	Male	**x**	0.0408	0.03088	
		y	-0.5254	0.11564	

GRF Medial	**Female**	**x**	-0.2116	0.10731	0.086
		y	0.0294	0.02134	0.798
	Male	**x**	-0.2803	0.12382	
		y	0.0271	0.03155	
GRF Posterior	**Female**	**x**	0.0352	0.02486	0.813
		y	0.3093	0.08935	0.015*
	Male	**x**	0.033	0.03051	
		y	0.3841	0.08634	

Table 10: Post hoc- Independent t-test results of group differences in absolute GRF at each target direction produced by older males and females.

	Direction	**Sex**	**Mean**	**SD**	***p* Value**
GRF_absolute	0	Male	42.538	8.41903	0.001*
		Female	32.992	7.93389	
Fy		Male	1.6559	2.53881	0.877
		Female	1.5550	1.13240	
Fx	30	Male	37.277	7.25093	0.001*
		Female	28.866	7.23965	
Fy		Male	-19.7214	5.97919	<0.001*
		Female	-12.2972	3.23105	
Fx	60	Male	22.699	4.35298	0.002*
		Female	17.660	4.65482	
Fy		Male	-35.9463	8.77954	<0.001*
		Female	-22.5498	5.54698	
Fx	90	Male	3.181	2.32180	0.160
		Female	2.223	1.56201	
Fy		Male	-41.5471	9.90249	<0.001*
		Female	-26.2324	6.41347	
Fx	120	Male	-9.889	5.57871	0.006*
		Female	-5.471	3.09844	
Fy		Male	-35.6983	8.82133	<0.001*
		Female	-22.5875	5.66988	
Fx	150	Male	-19.012	8.53739	0.001*
		Female	-10.676	5.37760	
Fy		Male	-19.6690	5.71959	<0.001*
		Female	-12.2462	3.11023	
Fx	180	Male	-22.441	10.00008	0.001*
		Female	-12.683	6.23323	
Fy		Male	2.1379	2.43136	0.609
		Female	1.8006	1.39051	
Fx	210	Male	-19.2167	8.75932	0.001*
		Female	-10.8402	5.28979	
Fy		Male	16.4951	4.05828	<0.001*
		Female	10.1619	4.09381	
Fx	240	Male	-10.061	5.68939	0.005*
		Female	-5.513	3.11872	
Fy		Male	26.6367	6.44857	<0.001*
		Female	16.4934	5.24820	
Fx	270	Male	2.547	2.32483	0.512
		Female	2.121	1.46627	
Fy		Male	30.4714	7.40956	<0.001*
		Female	18.8165	6.16228	

Fx	300	Male	22.277	4.15846	0.001*
		Female	17.137	4.50185	
Fy		Male	26.6145	6.48223	<0.001*
		Female	16.4065	5.41438	
Fx	330	Male	36.944	7.30490	0.002*
		Female	28.685	7.13259	
		Male	16.0676	3.86547	<0.001*
Fy		Female	10.1488	3.40291	

Table 11: MANOVA results of group differences in hip, knee, and ankle joint angles (°) at x-, y-, and z-axes. (adjusted alpha=0.017) *Note: x-axis +/- represents flexion/extension, y-axis +/- represents adduction/abduction, z-axis +/- represents internal rotation/external rotation.*

Joint (axis)	**Sex**	**Mean (SD)**	**Main Effect of Group- Wilks' Lambda (F value)**	***p* Value**	**Between-Group Differences (F value)**	***p* Value**
Hip(X)	Male Female	23.2(8.0) 24.8(10.0)	6.725	<0.001*	3.101	0.08
Hip(Y)	Male Female	-6.5(5.1) -4.7(3.5)			15.41	<0.001*
Hip(Z)	Male Female	2.2(10.0) 3.8(7.5)			3.119	0.078
Knee(X)	Male Female	17.6(5.4) 20.0(7.1)	15.843	<0.001*	15.805	<0.001*
Knee(Y)	Male Female	1.8(3.2) 0.18(3.6)			23.371	<0.001*
Knee(Z)	Male Female	7.8(15.2) 5.6(10.1)			2.772	0.097
Ankle(X)	Male Female	4.6(5.9) 7.8(5.5)	31.941	<0.001*	30.734	<0.001*
Ankle(Y)	Male Female	-7.2(11.2) -2.4(7.6)			24.958	<0.001*
Ankle(Z)	Male Female	-4.6(7.3) -6.8(6.1)			9.958	0.002*

Table 12: MANOVA results of group differences in hip, knee, and ankle joint moments (Nmm/kg) at x-, y-, and z- axes. (adjusted alpha =0.017) *Note: x-axis +/- represents flexion/extension, y-axis +/- represents adduction/abduction, z-axis +/- represents internal rotation/external rotation.*

Joint (axis)	**Sex**	**Mean (Standard Error)**	**Main Effect of Group- Wilks' Lambda (F value)**	***p* value**	**Between-Group Differences (F value)**	***p* value**
Hip(X)	Male Female	-375.9(16.4) -257.8(16.5)	22.019	<0.001*	38.197	<0.001*
Hip(Y)	Male Female	291.3(17.2) 192.9(16.8)			38.931	<0.001*
Hip(Z)	Male Female	-86.2(5.7) -80.7(5.1)			1.418	0.234
Knee(X)	Male Female	-22.8(10.1) -98.6(10.4)	14.798	<0.001*	29.515	<0.001*
Knee(Y)	Male Female	131.5(9.8) 83.1(9.8)			26.697	<0.001*

Knee(Z)	Male Female	-44.9(4.9) -48.2(3.6)			0.532	0.466
Ankle(X)	Male Female	-86.6(12.2) -78.5(16.6)	16.191	<0.001*	0.223	0.637
Ankle(Y)	Male Female	-53.0(5.8) -30.7(4.3)			13.317	<0.001*
Ankle(Z)	Male Female	-12.8(3.7) -46.6(4.6)			39.246	<0.001*

Table 13: Test of asymmetry results for each muscle in older males and females.

Muscle	**Sex**	***p* Value**
RF	Male Female	0.0568 0.710
VL	Male Female	0.957 0.250
VM	Male Female	0.969 0.395
BF	Male Female	0.0001* 0.022*
ST	Male Female	1.24E-06 2.81E-06*
LG	Male Female	0.002* 0.752
MG	Male Female	2.18E-05* 0.0001*
TFL	Male Female	0.536 0.379

Table 14: Independent t-test results of group differences in X_{EMG} of all muscles and independent t-test results of group differences in SI and Watson-Williams results of group differences in ϕ in muscles with asymmetrical activation patterns in older males and females. (RF included as males test of asymmetry was approaching significance (p=0.0568))

		X_{EMG}			**SI**			**ϕ**		
Muscle	**Sex**	**Mean**	**SD**	***p* value**	**Mean**	**SD**	**p value**	**Mean**	**R**	***p* value**
RF	Male Female	0.14 0.18	0.06 0.07	0.067	0.157 0.089	0.110 0.066	0.033*	105.5 109.2	9.1 3.3	0.930
VL	Male Female	0.35 0.33	0.15 0.15	0.640	0.104 0.114	0.064 0.080	N/A	218.8 273.0	3.0 6.0	N/A
VM	Male Female	0.27 0.26	0.16 0.11	0.928	0.112 0.115	0.071 0.099	N/A	215.6 273.8	1.2 6.8	N/A
BF	Male Female	0.42 0.31	0.22 0.13	0.084	0.306 0.219	0.148 0.130	0.074	198.8 183.7	15.6 14.9	0.160
ST	Male Female	0.39 0.29	0.18 0.17	0.121	0.330 0.289	0.139 0.120	0.356	248.0 257.2	16.1 15.5	0.360
LG	Male Female	0.18 0.18	0.09 0.07	0.887	0.258 0.103	0.144 0.044	<0.001*	180.6 189.2	10.1 5.6	0.760
MG	Male Female	0.29 0.23	0.16 0.09	0.175	0.327 0.298	0.165 0.161	0.594	156.8 143.5	14.1 13.6	0.350
TFL	Male Female	0.10 0.12	0.06 0.07	0.264	0.224 0.117	0.185 0.113	N/A	14.0 0.1	1.5 6.0	N/A

Table 15: Mixed model ANOVA results of group differences in level of normalised EMG by target direction for all eight muscles in older males and females.

	Main Effect of Direction		Interaction: Direction*Group	
Muscle	**F**	**p Value**	**F**	**p Value**
RF	2.489	0.031*	0.624	0.790
VL	2.883	0.017*	0.665	0.756
VM	2.610	0.024*	1.014	0.464
BF	7.549	<0.001*	3.052	0.012*
ST	9.099	<0.001*	0.720	0.709
LG	4.232	0.002*	0.917	0.540
MG	6.211	<0.001*	0.966	0.500
TFL	2.190	0.054	0.675	0.748

Table 16: Post hoc- Independent t-test results of between-group differences in muscle magnitude at each target direction. (RF and BF examined as they were approaching significance)

Muscle	Direction	Sex	Mean	SD	p Value
RF	0	Male	0.126	0.055	0.046*
		Female	0.170	0.070	
	30	Male	0.127	0.085	0.133
		Female	0.166	0.066	
	60	Male	0.125	0.074	0.108
		Female	0.166	0.072	
	90	Male	0.204	0.158	0.895
		Female	0.211	0.109	
	120	Male	0.184	0.115	0.567
		Female	0.205	0.093	
	150	Male	0.153	0.084	0.232
		Female	0.194	0.115	
	180	Male	0.118	0.057	0.045*
		Female	0.161	0.065	
	210	Male	0.116	0.052	0.016*
		Female	0.166	0.065	
	240	Male	0.110	0.054	0.009*
		Female	0.175	0.080	
	270	Male	0.112	0.051	0.009*
		Female	0.168	0.069	
	300	Male	0.124	0.057	0.028*
		Female	0.171	0.064	
	330	Male	0.129	0.053	0.048*
		Female	0.174	0.077	
BF	0	Male	0.224	0.153	0.907
		Female	0.230	0.132	
	30	Male	0.138	0.096	0.087
		Female	0.201	0.116	
	60	Male	0.245	0.140	0.946
		Female	0.242	0.115	
	90	Male	0.451	0.335	0.392
		Female	0.368	0.213	
	120	Male	0.537	0.370	0.140
		Female	0.382	0.214	
	150	Male	0.584	0.331	0.017*
		Female	0.361	0.158	

180	Male	0.554	0.296	0.063
	Female	0.387	0.204	
210	Male	0.561	0.359	0.027*
	Female	0.343	0.154	
240	Male	0.509	0.253	0.011*
	Female	0.322	0.138	
270	Male	0.442	0.277	0.076
	Female	0.307	0.137	
300	Male	0.434	0.307	0.062
	Female	0.279	0.132	
330	Male	0.320	0.197	0.321
	Female	0.260	0.152	

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Table 17: Results of one-way ANOVA with three planned comparisons in peak absolute and normalised knee extension, knee flexion, ankle plantar flexion, and hip abduction torques in male and female OA and male and female OC.

Movement	Group	Mean	SD	*p* Value
Hip Abduction (ABD)	FOA	51.191	15.18	0.021*
	MOA	65.183	15.80	
	FOA	51.191	15.18	0.988
	FOC	51.281	14.07	
	MOA	65.183	15.80	0.875
	MOC	66.0474	18.56	
Knee Extension (EXT)	FOA	76.391	24.81	0.066
	MOA	92.9593	22.68	
	FOA	76.391	24.81	0.547
	FOC	81.671653	20.12	
	MOA	92.9593	22.68	0.006*
	MOC	116.268663	27.91	
Knee Flexion (FLX)	FOA	51.373879	20.16	0.089
	MOA	62.505806	19.78	
	FOA	51.373879	20.16	0.74
	FOC	49.257447	12.66	
	MOA	62.505806	19.78	0.595
	MOC	65.696632	17.41	
Ankle Plantar Flexion (PLA)	FOA	57.1039	20.79	0.151
	MOA	67.901063	19.03	
	FOA	57.1039	20.79	0.605
	FOC	53.296771	18.53	
	MOA	67.901063	19.03	0.283
	MOC	75.204668	21.01	
ABD_normalised	FOA	.707250	0.18	0.053
	MOA	.901725	0.26	
	FOA	.707250	0.18	0.518
	FOC	.770559	0.36	
	MOA	.901725	0.26	0.488
	MOC	.837837	0.24	
EXT_normalised	FOA	1.051714	0.30	0.077

	MOA	1.274544	0.35	
	FOA FOC	1.051714 1.377494	0.30 0.31	0.01*
	MOA MOC	1.274544 1.489658	0.35 0.37	0.066
FLX_normalised	FOA MOA	.696671 .860500	0.24 0.27	0.048
	FOA FOC	.696671 .826871	0.24 0.16	0.108
	MOA MOC	.860500 .831816	0.27 0.21	0.704
PLA_normalised	FOA MOA	.804723 .941294	0.28 0.31	0.232
	FOA FOC	.804723 .915476	0.28 0.35	0.325
	MOA MOC	.941294 .953547	0.31 0.27	0.906

Table 18: A) MANOVA (Wilks' Lambda) results for absolute and normalised GRF in older males and females, B) between-group effects of absolute and normalised GRF for each paired comparison. (adjusted alpha=0.025)

A.

	Group	**Main Effect of Group**		**Interaction**	
		F	***p* Value**	**F**	***p* Value**
GRF Absolute	FOAMOA FOAFOC MOAMOC	25.226 5.155 19.948	<0.001* 0.006* <0.001*	0.920 0.848 0.708	0.569 0.666 0.835
GRF Lateral	FOAMOA FOAFOC MOAMOC	1.229 3.001 0.856	0.309 0.066 0.434		
GRF Anterior	FOAMOA FOAFOC MOAMOC	0.273 1.477 0.603	0.763 0.246 0.553		
GRF Medial	FOAMOA FOAFOC MOAMOC	2.958 3.446 0.756	0.069 0.046 0.478		
GRF Posterior	FOAMOA FOAFOC MOAMOC	1.936 1.838 0.811	0.164 0.178 0.453		

B.

	Group	**GRF-axis**	**Mean**	**SD**	**F**	***p* Value**
GRF Absolute	**FOA-MOA**	**x**			32.034	<0.001*
		y			27.751	<0.001*
	FOA-FOC	**x**			0.217	0.641
		y			10.179	0.002*
	MOA-MOC	**x**			9.384	0.002*
		y			37.413	<0.001*
GRF	**FOA**	**x**	.5180	.17535	1.525	0.227

Lateral		**y**	.0065	.02524	1.831	0.187
	MOA	**x**	.6000	.18651		
		y	.0198	.02813		
	FOA	**x**	.5180	.17535		
		y	.0065	.02524		
	FOC	**x**	.5478	.11897	0.316	0.578
		y	.0254	.01699	6.149	0.019*
	MOA	**x**	.6000	.18651		
		y	.0198	.02813		
	MOC	**x**	.5374	.10274	1.575	0.218
		y	.0214	.03367	0.022	0.882
GRF Anterior	**FOA**	**x**	.0270	.03022	0.062	0.805
		y	-.5054	.18213	0.53	0.472
	MOA	**x**	.0300	.03453		
		y	-.5481	.13814		
	FOA	**x**	.0270	.03022		
		y	-.5054	.18213		
	FOC	**x**	.0366	.02547	0.931	0.343
		y	-.4381	.11652	1.556	0.222
	MOA	**x**	.0300	.03453		
		y	-.5481	.13814		
	MOC	**x**	.0408	.03088	0.962	0.334
		y	-.5254	.11564	0.281	0.600
GRF Medial	**FOA**	**x**	-.2200	.09839	5.243	0.030
		y	.0056	.02835	1.145	0.294
	MOA	**x**	-.3205	.13600		
		y	.0172	.03058		
	FOA	**x**	-.2200	.09839		
		y	.0056	.02835		
	FOC	**x**	-0.2116	0.10731	0.051	0.823
		y	.0294	.02134	7.137	0.012*
	MOA	**x**	-.3205	.13600		
		y	.0172	.03058		
	MOC	**x**	-.2803	.12382	0.837	0.367
		y	.0271	.03155	0.883	0.354
GRF Posterior	**FOA**	**x**	.0178	.03464	0.046	0.831
		y	.3104	.12243	3.904	0.058
	MOA	**x**	.0204	.03062		
		y	.3975	.11884		
	FOA	**x**	.0178	.03464		
		y	.3104	.12243		
	FOC	**x**	.0352	.02486	2.642	0.115
		y	.3093	.08935	0.001	0.977
	MOA	**x**	.0204	.03062		
		y	.3975	.11884		
	MOC	**x**	.0330	.03051	1.476	0.233
		y	.3841	.08634	0.15	0.701

Table 19: Post hoc- Independent t-test results of group differences in absolute GRF at each target direction for each paired comparison.

Direction		**Group**	**Mean**	**SD**	***p* Value**
0	**Fx**	FOA	32.6719	9.37109	0.105

		MOA	38.1283	10.58224	
		FOA FOC	32.6719 32.9919	9.37109 7.93389	0.922
		MOA MOC	38.1283 42.5380	10.58224 8.41903	0.157
	Fy	FOA MOA	.4407 1.2212	1.64916 1.72382	0.216
		FOA FOC	.4407 1.5550	1.64916 1.13240	0.043*
		MOA MOC	1.2212 1.6559	1.72382 2.53881	0.553
30	**Fx**	FOA MOA	28.5099 33.4983	8.21929 9.04721	0.090
		FOA FOC	28.5099 28.8663	8.21929 7.23965	0.901
		MOA MOC	33.4983 37.2771	9.04721 7.25093	0.165
	Fy	FOA MOA	-15.1763 -17.1221	4.65353 4.84620	0.275
		FOA FOC	-15.1763 -12.2972	4.65353 3.23105	0.103
		MOA MOC	-17.1221 -19.7214	4.84620 5.97919	0.118
60	**Fx**	FOA MOA	16.8171 20.0797	5.39266 5.66523	0.079
		FOA FOC	16.8171 17.6599	5.39266 4.65482	0.642
		MOA MOC	20.0797 22.6986	5.66523 4.35298	0.127
	Fy	FOA MOA	-27.1623 -30.6057	7.96085 7.39428	0.217
		FOA FOC	-27.1623 -22.5498	7.96085 5.54698	0.095
		MOA MOC	-30.6057 -35.9463	7.39428 8.77954	0.041*
90	**Fx**	FOA MOA	1.7205 1.8955	2.00050 2.06698	0.813
		FOA FOC	1.7205 2.2225	2.00050 1.56201	0.493
		MOA MOC	1.8955 3.1810	2.06698 2.32180	0.065
	Fy	FOA MOA	-31.6462 -35.2913	9.31674 8.63058	0.255
		FOA FOC	-31.6462 -26.2324	9.31674 6.41347	0.089
		MOA MOC	-35.2913 -41.5471	8.63058 9.90249	0.038*
120	**Fx**	FOA MOA	-6.8578 -9.6037	3.54436 4.62195	0.077
		FOA FOC	-6.8578 -5.4714	3.54436 3.09844	0.262

		MOA	-9.6037	4.62195	0.870
		MOC	-9.8887	5.57871	
	Fy	FOA	-26.6154	8.87229	0.190
		MOA	-30.4188	7.64906	
		FOA	-26.6154	8.87229	0.160
		FOC	-22.5875	5.66988	
		MOA	-30.4188	7.64906	0.052
		MOC	-35.6983	8.82133	
150	**Fx**	FOA	-12.0352	5.11514	0.028*
		MOA	-17.7348	7.48563	
		FOA	-12.0352	5.11514	0.587
		FOC	-10.6759	5.37760	
		MOA	-17.7348	7.48563	0.588
		MOC	-19.0122	8.53739	
	Fy	FOA	-15.4672	5.43284	0.370
		MOA	-17.0651	4.62730	
		FOA	-15.4672	5.43284	0.070
		FOC	-12.2462	3.11023	
		MOA	-17.0651	4.62730	0.117
		MOC	-19.6690	5.71959	
180	**Fx**	FOA	-13.9401	6.01544	0.028*
		MOA	-20.4683	8.28447	
		FOA	-13.9401	6.01544	0.663
		FOC	-12.6832	6.23323	
		MOA	-20.4683	8.28447	0.468
		MOC	-22.4409	10.00008	
	Fy	FOA	.3597	1.86670	0.355
		MOA	1.0247	1.87756	
		FOA	.3597	1.86670	0.045*
		FOC	1.8006	1.39051	
		MOA	1.0247	1.87756	0.097
		MOC	2.1379	2.43136	
210	**Fx**	FOA	-12.0351	5.34826	0.029*
		MOA	-17.7848	7.53308	
		FOA	-12.0351	5.34826	0.639
		FOC	-10.8402	5.28979	
		MOA	-17.7848	7.53308	0.550
		MOC	-19.2167	8.75932	
	Fy	FOA	10.1175	3.67992	0.021*
		MOA	13.4710	3.60343	
		FOA	10.1175	3.67992	0.975
		FOC	10.1619	4.09381	
		MOA	13.4710	3.60343	0.025*
		MOC	16.4951	4.05828	
240	**Fx**	FOA	-6.8247	3.68529	0.047*
		MOA	-10.0409	4.75891	
		FOA	-6.8247	3.68529	0.301
		FOC	-5.5130	3.11872	
		MOA	-10.0409	4.75891	0.991
		MOC	-10.0610	5.68939	
	Fy	FOA	17.0199	5.65798	0.017*

		MOA	22.2008	5.59996	
		FOA	17.0199	5.65798	0.802
		FOC	16.4934	5.24820	
		MOA	22.2008	5.59996	0.027*
		MOC	26.6367	6.44857	
270	**Fx**	FOA	1.1281	2.30016	0.821
		MOA	1.2957	1.87290	
		FOA	1.1281	2.30016	0.178
		FOC	2.1214	1.46627	
		MOA	1.2957	1.87290	0.073
		MOC	2.5467	2.32483	
	Fy	FOA	19.5546	6.15765	0.023*
		MOA	25.1335	6.06097	
		FOA	19.5546	6.15765	0.755
		FOC	18.8165	6.16228	
		MOA	25.1335	6.06097	0.019*
		MOC	30.4714	7.40956	
300	**Fx**	FOA	16.5943	5.12494	0.078
		MOA	19.6971	5.22609	
		FOA	16.5943	5.12494	0.752
		FOC	17.1370	4.50185	
		MOA	19.6971	5.22609	0.113
		MOC	22.2773	4.15846	
	Fy	FOA	17.0420	5.54716	0.021*
		MOA	22.0669	5.58540	
		FOA	17.0420	5.54716	0.763
		FOC	16.4065	5.41438	
		MOA	22.0669	5.58540	0.024*
		MOC	26.6145	6.48223	
330	**Fx**	FOA	27.9999	8.08672	0.073
		MOA	33.2436	8.94211	
		FOA	27.9999	8.08672	0.810
		FOC	28.6850	7.13259	
		MOA	33.2436	8.94211	0.170
		MOC	36.9441	7.30490	
	Fy	FOA	10.0552	3.52699	0.016*
		MOA	13.4170	3.91228	
		FOA	10.0552	3.52699	0.944
		FOC	10.1488	3.40291	
		MOA	13.4170	3.91228	0.038*
		MOC	16.0676	3.86547	

Table 20: MANOVA results of group differences in hip, knee, and ankle joint angles at x-, y-, and z- axes for each paired comparison. (adjusted alpha=0.017) *Note: x-axis +/- represents flexion/extension, y-axis +/- represents adduction/abduction, z-axis +/- represents internal rotation/external rotation.*

Joint (axis)	**Mean (SD)**	**Main effect of Group- Wilks' Lambda (F value)**	***p* Value**	**Between-group Effect (F value)**	***p* Value**
Hip(X) FOA	26.3(10.6)				
MOA	25.5(11.1)	56.053	<0.001*	0.480	0.489

	FOC	24.8(10.0)	20.646	<0.001*	1.758	0.186
	MOC	23.2(8.0)	8.067	<0.001*	5.784	0.017
Hip(Y)	FOA	-1.6(5.7)				
	MOA	-8.8(5.5)			135.973	<0.001*
	FOC	-4.7(3.6)			35.279	<0.001*
	MOC	-6.5(5.1)			18.849	<0.001*
Hip(Z)	FOA	-0.06(10.1)				
	MOA	1.9(7.7)			4.136	0.043
	FOC	3.8(7.5)			15.663	<0.001*
	MOC	2.2(10.0)			0.107	0.744
Knee(X)	FOA	19.2(7.8)				
	MOA	18.4(8.3)	45.7	<0.001*	0.784	0.377
	FOC	20.0(7.1)	12.079	<0.001*	0.901	0.343
	MOC	17.6(5.5)	9.412	<0.001*	1.506	0.22
Knee(Y)	FOA	-2.3(5.2)				
	MOA	2.8(4.1)			103.947	<0.001*
	FOC	0.18(3.6)			26.31	<0.001*
	MOC	1.8(3.2)			8.267	0.004*
Knee(Z)	FOA	7.3(10.6)				
	MOA	12.8(13.2)			17.14	<0.001*
	FOC	5.6(10.1)			2.136	0.145
	MOC	7.8(15.2)			12.42	<0.001*
Ankle(X)	FOA	9.0(6.2)				
	MOA	11.2(10.9)	23.96	<0.001*	4.561	0.033
	FOC	7.8(5.5)	7.77	<0.001*	3.409	0.066
	MOC	4.6(5.9)	21.87	<0.001*	58.27	<0.001*
Ankle(Y)	FOA	-5.3(14.0)				
	MOA	-12.1(12.0)			22.972	<0.001*
	FOC	-2.4(7.6)			6.021	0.015*
	MOC	-7.2(11.2)			18.711	<0.001*
Ankle(Z)	FOA	-3.9(8.6)				
	MOA	-11.2(11.4)			41.09	<0.001*
	FOC	-6.8(6.1)			11.471	0.001*
	MOC	-4.6(7.3)			49.59	<0.001*

Table 21: MANOVA results of group differences in hip, knee, and ankle joint moments (Nmm/kg) at x-, y-, and z- axes for each paired comparison. (adjusted alpha=0.017) *Note: x-axis +/- represents*

flexion/extension, y-axis +/- represents adduction/abduction, z-axis +/- represents internal rotation/external rotation.

Joint (axis)		**Mean(Standard Error)**	**Main Effect of Group- Wilks' Lambda (F value)**	***p* Value**	**Between-group effect (F value)**	***p* Value**
Hip(X)	FOA	-266.48 (15.12)				
	MOA	-363.29(18.39)	33.286	<0.001*	21.235	<0.001*
	FOC	-257.81(16.47)	6.658	<0.001*	0.208	0.649
	MOC	-375.87(16.36)	2.918	0.034	0.385	0.535
Hip(Y)	FOA	145.12(15.30)				
	MOA	279.08(15.31)			78.675	<0.001*
	FOC	192.91(16.81)	`		12.045	0.001*
	MOC	291.33(17.18)			0.562	0.454
Hip(Z)	FOA	-64.66(4.73)				
	MOA	-69.99(6.14)			0.780	0.378
	FOC	-80.73(5.08)			14.988	<0.001*
	MOC	-86.24(5.72)			7.816	0.005*
Knee(X)	FOA	-69.75(9.71)				
	MOA	-51.51(10.03)	1.234	0.297	1.785	0.183
	FOC	-98.62(10.36)	10.73	<0.001*	4.319	0.039
	MOC	-22.77(10.13)	8.767	<0.001*	4.429	0.036
Knee(Y)	FOA	99.25(9.6)				
	MOA	101.60(10.82)			0.041	0.839
	FOC	-83.11(9.78)			2.937	0.088
	MOC	131.54(9.78)			7.648	0.006*
Knee(Z)	FOA	-27.42(3.55)				
	MOA	-31.37(4.29)			0.826	0.364
	FOC	-48.18(3.61)			31.466	0.833
	MOC	-4493(4.91)			8.089	0.005*
Ankle(X)	FOA	-137.54(14.24)				
	MOA	-56.23(12.38)	14.139	<0.001*	21.983	<0.001*
	FOC	-78.49(16.62)	10.287	<0.001*	9.609	0.002*
	MOC	-86.55(12.16)	2.697	0.046	3.722	0.054
Ankle(Y)	FOA	-13.18(5.41)				
	MOA	-34.24(6.79)			6.782	0.01*
	FOC	-30.73(4.27)			7.718	0.006*
	MOC	-53.02(5.75)			6.546	0.011*
Ankle(Z)	FOA	-20.86(4.41)				

MOA	-11.79(5.22)			1.959	0.002*
FOC	-46.61(4.57)			19.983	<0.001*
MOC	-12.81(3.74)			0.030	0.863

Table 22: Test of asymmetry results for each muscle in male OA and female OA. (Male and Female OC results in Table 12)

Muscle	Group	*p* Value
RF	MOA	0.717
	FOA	0.923
VL	MOA	0.799
	FOA	0.565
VM	MOA	0.711
	FOA	0.662
BF	MOA	1.67E-05*
	FOA	0.019*
ST	MOA	7.06E-05*
	FOA	0.0001*
LG	MOA	0.293
	FOA	0.718
MG	MOA	0.003*
	FOA	0.026*
TFL	MOA	0.757
	FOA	0.977

Table 23: One-way ANOVA with three paired comparisons results of group differences in X_{EMG} in all muscles, and one-way ANOVA with three paired comparison results of group differences in SI and Watson-Williams results of ϕ in muscles with asymmetrical activation patterns in male and female OA and male and female OC. (RF included in MOA-MOC comparison as MOC's test of asymmetry was approaching significance (p=0.0568))

		X_{EMG}			SI			ϕ		
Muscle	Group	Mean	SD	*p* Value	Mean	SD	*p* Value	Mean	R	*p* Value
RF	FOA	0.24	0.11	0.441	0.082	0.041	N/A	107.6	2.5	
	MOA	0.21	0.10		0.106	0.059		47.0	7.0	N/A
	FOA	0.24	0.11	0.072	0.082	0.041	N/A	107.6	2.5	
	FOC	0.18	0.07		0.089	0.066		109.2	3.3	N/A
	MOA	0.21	0.10	.016*	0.106	0.059	0.102	47.0	7.0	
	MOC	0.14	0.06		0.157	0.110		105.5	9.1	0.051
VL	FOA	0.36	0.15	0.725	0.106	0.051	N/A	254.6	4.7	
	MOA	0.38	0.15		0.108	0.070		316.1	2.3	N/A
	FOA	0.36	0.15	0.550	0.106	0.051	N/A	254.6	4.7	
	FOC	0.33	0.15		0.114	0.080		273.0	6.0	N/A
	MOA	0.38	0.15	0.591	0.108	0.070	N/A	316.1	2.3	
	MOC	0.35	0.15		0.104	0.064		218.8	3.0	N/A
VM	FOA	0.28	0.11	0.504	0.080	0.060	N/A	261.4	2.8	
	MOA	0.31	0.12		0.070	0.058		329.2	5.5	N/A
	FOA	0.28	0.11	0.712	0.080	0.060	N/A	261.4	2.8	
	FOC	0.26	0.11		0.115	0.099		273.8	6.8	N/A
	MOA	0.31	0.12	0.313	0.070	0.058	N/A	329.2	5.5	
	MOC	0.27	0.16		0.112	0.071		215.6	1.2	N/A
BF	FOA	0.51	0.32	0.429	0.177	0.066	.013*	205.6	11.2	

	MOA	0.43	0.25		0.273	0.123		191.6	11.8	0.380
	FOA	0.51	0.32	.041*	0.177	0.066	0.256	205.6	11.2	
	FOC	0.31	0.13		0.219	0.130		183.7	14.9	0.090
	MOA	0.43	0.25	0.918	0.273	0.123	0.475	191.6	11.8	
	MOC	0.42	0.22		0.306	0.148		198.8	15.6	0.600
ST	FOA	0.29	0.19	0.753	0.227	0.075	0.229	255.6	13.1	
	MOA	0.32	0.26		0.278	0.104		260.1	13.8	0.650
	FOA	0.29	0.19	0.997	0.227	0.075	0.141	255.6	13.1	
	FOC	0.29	0.17		0.289	0.120		257.2	15.5	0.850
	MOA	0.32	0.26	0.306	0.278	0.104	0.191	260.1	13.8	
	MOC	0.39	0.18		0.330	0.139		248.0	16.1	0.280
LG	FOA	0.22	0.12	0.138	0.123	0.080	N/A	169.5	4.0	
	MOA	0.16	0.10		0.190	0.086		190.2	9.5	N/A
	FOA	0.22	0.12	0.261	0.123	0.080	N/A	169.5	4.0	
	FOC	0.18	0.07		0.103	0.044		189.2	5.6	N/A
	MOA	0.16	0.10	0.593	0.190	0.086	0.152	190.2	9.5	
	MOC	0.18	0.09		0.248	0.144		180.6	10.1	0.640
MG	FOA	0.35	0.18	.020*	0.195	0.145	0.324	177.7	8.5	
	MOA	0.22	0.13		0.252	0.158		161.0	9.8	0.450
	FOA	0.35	0.18	.031*	0.195	0.145	0.075	177.7	8.5	
	FOC	0.23	0.09		0.298	0.161		143.5	13.6	0.069
	MOA	0.22	0.13	0.151	0.252	0.158	0.168	161.0	9.8	
	MOC	0.29	0.16		0.327	0.165		156.8	14.1	0.820
TFL	FOA	0.14	0.07	0.906	0.082	0.034	N/A	299.3	2.9	
	MOA	0.14	0.11		0.157	0.142		48.4	2.4	N/A
	FOA	0.14	0.07	0.472	0.082	0.034	N/A	299.3	2.9	
	FOC	0.12	0.08		0.117	0.113		0.1	6.0	N/A
	MOA	0.14	0.11	0.124	0.157	0.142	N/A	48.4	2.4	
	MOC	0.12	0.07		0.224	0.185		14.0	1.5	N/A

Table 24: Mixed model ANOVA results of group differences in level of normalised EMG by target direction for all eight muscles for each paired comparison. (adjusted alpha=0.025)

Muscle	**Group**	**Main Effect of Direction (F value)**	***p* Value**	**Interaction: Direction* Group (F value)**	***p* Value**
RF	FOAMOA	3.270	0.013*	1.348	0.277
	FOAFOC	3.053	0.016*	0.702	0.722
	MOAMOC	2.941	0.015*	1.561	0.180
VL	FOAMOA	2.694	0.03*	1.068	0.435
	FOAFOC	2.882	0.021*	0.847	0.600
	MOAMOC	3.130	0.011*	0.737	0.693
VM	FOAMOA	2.301	0.060	1.034	0.460
	FOAFOC	2.213	0.062	0.953	0.516
	MOAMOC	2.956	0.015*	1.240	0.320
BF	FOAMOA	9.294	<0.001*	2.091	0.080
	FOAFOC	7.435	<0.001*	1.961	0.095
	MOAMOC	4.832	0.001*	1.141	0.379
ST	FOAMOA	5.301	0.001*	1.337	0.282
	FOAFOC	6.410	<0.001*	0.752	0.680
	MOAMOC	9.608	<0.001*	0.728	0.702
LG	FOAMOA	3.087	0.017*	0.938	0.529
	FOAFOC	2.904	0.021*	1.360	0.268
	MOAMOC	4.242	0.002*	0.570	0.833

MG	FOAMOA	5.285	0.001*	1.339	0.281
	FOAFOC	3.713	0.006*	1.749	0.137
	MOAMOC	5.243	<0.001*	1.400	0.238
TFL	FOAMOA	3.200	0.016*	0.751	0.680
	FOAFOC	1.406	0.251	1.043	0.452
	MOAMOC	3.417	0.007*	0.799	0.640

Table 25: Post hoc- Independent t-test results for between-group differences in muscle magnitude by direction.

Muscle	Direction	Sex	Mean	SD	p Value
RF	0	FOA	.237683	.1138757	.053
		FOC	.170436	.0701752	
		MOA	.215981	.1065310	0.006*
		MOC	.126185	.0554993	
	30	FOA	.231444	.1215719	.068
		FOC	.166391	.0660964	
		MOA	.212112	.0920931	0.008*
		MOC	.126597	.0848931	
	60	FOA	.212815	.0956136	.134
		FOC	.166365	.0723397	
		MOA	.214214	.1118209	0.0095*
		MOC	.125334	.0742627	
	90	FOA	.247750	.0912406	.317
		FOC	.210550	.1086809	
		MOA	.243262	.1197738	.429
		MOC	.204427	.1577215	
	120	FOA	.267473	.1232524	.118
		FOC	.204931	.0929035	
		MOA	.237958	.1271526	.207
		MOC	.184357	.1154201	
	150	FOA	.239831	.1060722	.267
		FOC	.194317	.1154456	
		MOA	.209436	.1140439	.107
		MOC	.153024	.0836660	
	180	FOA	.245622	.1253056	0.0348*
		FOC	.161280	.0654450	
		MOA	.198135	.0993292	0.009*
		MOC	.118119	.0570267	
	210	FOA	.244285	.1156943	0.036*
		FOC	.166334	.0647508	
		MOA	.194649	.1065768	0.014*
		MOC	.116219	.0520280	
	240	FOA	.252798	.1574831	.109
		FOC	.174834	.0800360	
		MOA	.207500	.1226256	0.008*
		MOC	.110041	.0535516	
	270	FOA	.236987	.1268536	.083
		FOC	.167889	.0687193	
		MOA	.200490	.1119458	0.008*
		MOC	.111634	.0506939	
	300	FOA	.247135	.1244208	.052
		FOC	.170789	.0641934	

		MOA	.200263	.0966769	0.0106*
		MOC	.123635	.0569533	
	330	FOA	.236896	.1009699	.060
		FOC	.174368	.0770353	
		MOA	.201707	.0997866	0.0156*
		MOC	.128720	.0526761	
BF	0	FOA	.362219	.2128619	.056
		FOC	.230118	.1324258	
	30	FOA	.325374	.2581854	.114
		FOC	.201351	.1161461	
	60	FOA	.466992	.4240633	.074
		FOC	.242020	.1146002	
	90	FOA	.521549	.4030747	.215
		FOC	.368379	.2129961	
	120	FOA	.557492	.3799264	.117
		FOC	.382482	.2139254	
	150	FOA	.627393	.4503972	.051
		FOC	.360989	.1575767	
	180	FOA	.626722	.4501516	.083
		FOC	.387264	.2040340	
	210	FOA	.599207	.3774010	0.0296*
		FOC	.343255	.1542528	
	240	FOA	.580651	.3469371	0.018*
		FOC	.322121	.1375258	
	270	FOA	.563803	.2940724	0.0076*
		FOC	.306701	.1369249	
	300	FOA	.484677	.2609374	0.015*
		FOC	.278935	.1323079	
	330	FOA	.415582	.1991911	0.0196*
		FOC	.259870	.1520744	
MG	0	FOA	.254999	.1420617	.059
		MOA	.160530	.1213600	
		FOA	.254999	.1420617	.205
		FOC	.191378	.1308317	
	30	FOA	.259380	.1834517	0.036*
		MOA	.137404	.0914477	
		FOA	.259380	.1834517	.052
		FOC	.145039	.1309507	
	60	FOA	.303977	.2130156	.088
		MOA	.191543	.1301680	
		FOA	.303977	.2130156	.056
		FOC	.185331	.1129053	
	90	FOA	.404291	.2199031	.058
		MOA	.264447	.1660957	
		FOA	.404291	.2199031	.324
		FOC	.337114	.1520168	
	120	FOA	.484884	.2746097	0.036*
		MOA	.304076	.1703252	
		FOA	.484884	.2746097	.111
		FOC	.346144	.1947500	
	150	FOA	.417843	.2273778	.109

	MOA	.295221	.1773672	
	FOA	.417843	.2273778	.318
	FOC	.342656	.1852498	
180	FOA	.427858	.2443200	.074
	MOA	.278781	.1958291	
	FOA	.427858	.2443200	.107
	FOC	.305698	.1635531	
210	FOA	.356932	.2004364	.108
	MOA	.244602	.1704652	
	FOA	.356932	.2004364	0.044*
	FOC	.230104	.0987789	
240	FOA	.341825	.2160936	.082
	MOA	.217991	.1583382	
	FOA	.341825	.2160936	0.0187*
	FOC	.181055	.0902158	
270	FOA	.325974	.1911277	.057
	MOA	.205595	.1395088	
	FOA	.325974	.1911277	0.0255*
	FOC	.183777	.1238036	
300	FOA	.295573	.1897471	.100
	MOA	.193268	.1384846	
	FOA	.295573	.1897471	0.023*
	FOC	.164134	.1128024	
330	FOA	.305508	.1834652	0.024*
	MOA	.169131	.1080985	
	FOA	.305508	.1834652	0.030*
	FOC	.182568	.1142285	

Table 26: Intra-Class Correlations (ICC), Confidence Intervals (CI) and Standard Error of Measurement (SEM) in brackets of each muscle in male and female OA. (OC results previously reported in Article 1). (LB represents Lower Bound CI, UP represents Upper Bound CI))

		RF	VL	VM	BF	ST	LG	MG	TFL
FOA	ICC	0.167	0.584	0.513	0.869	0.923	0.61	0.841	0.376
	LB	-0.736	0.134	-0.015	0.726	0.84	0.187	0.668	-0.306
	UP	0.716	0.858	0.834	0.955	0.974	0.867	0.946	0.787
	SD	0.1148	0.1654	0.1205	0.3510	0.2136	0.1373	0.2140	0.0724
	SEM	**0.1047**	**0.1067**	**0.0841**	**0.1270**	**0.0593**	**0.0857**	**0.0854**	**0.0572**
MOA	ICC	0.528	0.053	0.685	0.882	0.943	0.322	0.876	0.045
	LB	0.022	-0.962	0.347	0.754	0.881	-0.409	0.743	-0.985
	UB	0.839	0.677	0.893	0.96	0.98	0.769	0.958	0.674
	SD	0.1073	0.1709	0.1287	0.3295	0.2833	0.1217	0.1552	0.1115
	SEM	**0.0737**	**0.1663**	**0.0722**	**0.1132**	**0.0676**	**0.1002**	**0.0546**	**0.1089**

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Table 27: MANOVA results of mean quadriceps muscle contributions to maximum knee extension torque.

Muscle	Main Effect of Group- Wilks' Lambda (F value)	p Value	Between-group Effects (F value)	*p* Value
RF	0.466	0.832	0.587	0.626
VL			0.196	0.899
VM			0.465	0.708

Table 28: MANOVA results of mean knee flexor muscle contributions to maximum knee flexion torque.

Muscle	Main Effect of Group- Wilks' Lambda (F value)	p Value	Between-group Effects (F value)	*p* Value
BF	1.338	0.224	2.322	0.085
ST			1.563	0.209
LG			1.434	0.243
MG			1.315	0.279

Table 29: One-way ANOVA result of between-group differences of knee extension and knee flexion level of voluntary activation.

	Group	Mean	SD	Between-group Effect (F value)	*p* Value
Knee Extension	FOA	0.613	0.158	6.519	0.001*
	MOA	0.646	0.161		
	FOC	0.600	0.115		
	MOC	0.826	0.202		
Knee Flexion	FOA	0.455	0.130	0.962	0.417
	MOA	0.408	0.125		
	FOC	0.394	0.084		
	MOC	0.440	0096		