Muscle force contributions to knee joint loading

Submitted by

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Statement of authorship and sources

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No other person's work has been used without due acknowledgment in the main text of the thesis. All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

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Publications related to thesis

1. **Maniar, N,** Shield, A.J, Williams, M.D, Timmins, R.G, & Opar, D.A. (2016) Hamstring strength and flexibility after hamstring strain injury: a systematic review and meta-analysis. *British Journal of Sports Medicine*, *50*(15). 909-920. doi: 10.1136/bjsports-2015-095311.
2. **Maniar, N,** Schache, A.G, Sritharan, P, & Opar, D.A. Non-knee-spanning muscles contribute to tibiofemoral shear as well as valgus and rotational joint reaction moments during unanticipated sidestep cutting. *Scientific Reports*, *8*(1). 2501. doi: 10.1038/s41598-017-19098-9.

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Other relevant book chapters (in press)

1. **Maniar, N,** Duncan, K, & Opar, D.A. Systematically searching and reviewing the literature. *Research Methods in Physical Activity and Health.* 1st ed. Editors Prof Stephen Bird and Prof John Hawley. Publisher Routledge.

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3. **Maniar, N,** Schache, A.G, Beerworth, K.A, & Opar, D.A. Non-knee-spanning muscles contribute to knee joint valgus and shear loading. *International Society of Biomechanics 2017* – Brisbane, July 2017.

Software packages

1. **Maniar, N.** (2017). biomechanics. R package version 0.1.

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Abstract

Anterior cruciate ligament (ACL) injuries are one of the most common knee injuries suffered by athletic populations. ACL injuries are particularly burdensome due to potential surgical requirements, extensive rehabilitation time and associated financial costs for the individual and the community. Additionally, ACL injuries are associated with increased risk of early onset knee osteoarthritis. As such, ACL injury preventative and rehabilitative strategies are of paramount importance.

ACL injuries typically occur during non-contact dynamic tasks, such as unanticipated sidestep cutting. At the time of injury, the knee joint experiences relatively large degrees of knee valgus and rotation (either internal or external) and high mechanical loads. These loading patterns, along with the anterior shear force, are known to increase loads on the ACL, especially in combination with each other. Muscles produce forces that can cause and oppose these knee joint loads, and therefore play a critical role in dictating the size and the nature of the loads experienced by the ACL. Prior research has investigated the role of muscle force in ACL load development, and has indicated that the hamstrings are most capable of reducing ACL loads. Subsequently, any pathology that may influence hamstring function may increase the risk of ACL injury.

Some studies have shown that participants with a history of hamstring strain injury (HSI) have lower knee flexor strength and hamstring muscle activation compared to healthy legs. Consequently, a relationship between prior HSI and ACL injury could exist. However, establishing this relationship is difficult due to the relatively low incidence of ACL injury. Subsequently, prospective studies aiming to investigate this relationship would be very costly, due to the requirement of very large sample sizes and long follow-up periods. Additionally, such a relationship would depend on the functional role of the hamstring muscle group during potentially ACL-injurious manoeuvres such as sidestep cutting, which has not been fully elucidated. Furthermore, given the multi-planar demands of tasks that place the ACL at risk of injury, better understanding the contribution of the individual hamstring muscles to knee joint loading relative to the other lower-limb muscles is imperative.

Musculoskeletal simulation offers the ability to analyse cause-effect relationships between muscle force development and joint loading whilst accounting for whole body kinematics. This analysis could not only reveal the true potential of the hamstring muscles in protecting the ACL, but could also elucidate the role of other muscles which have been less studied.

The purpose of this doctoral thesis was to explore the relationship between muscle forces in the development of knee joint loading during potentially injurious manoeuvres, as this knowledge may be used to inform interventions that aim to reduce ACL injury risk. Given recent hypotheses suggesting a possible association between prior injury to the hamstrings and an increased risk of ACL injury and based on the current literature, which indicates that the hamstrings are one of the most important muscle groups for unloading the ACL, the focus of the first study (Chapter 4) was to determine the impact of HSI on hamstring function. Specifically, a systematic review and meta-analysis was used to compare knee flexor strength and flexibility in previously injured legs to the uninjured contralateral leg. It was found that deficits in concentric and eccentric strength (and associated hamstring to quadriceps strength ratios) were present at and after return to play. Isometric strength deficits were also present after HSI, but these recovered within 20-30 days. Hamstring flexibility deficits were also found after HSI, but these recovered within 40-50 days post injury. A secondary aim of this study was to document the totality of measures reported in the literature that have been taken in previously injured hamstrings. The review revealed that knee flexor and extensor strength were the most commonly assessed variables in participants with previously injured hamstrings and that there are few studies which examine the function of other lower-limb muscles. Furthermore, there was limited information examining multi-planar movements. The findings of the review highlighted the need to better understand how the hamstrings contribute to knee joint loading, relative to the contribution of other lower-limb muscles, to better guide future work examining the link between prior HSI and future ACL injury.

The conclusions obtained from Chapter 4 informed the direction of the three subsequent chapters. The focus of the second study (Chapter 5) was to investigate the contribution of the hamstrings to ACL loading during the weight acceptance phase of an unanticipated sidestep cut relative to other lower-limb muscles. A musculoskeletal modelling approach was used to determine how different lower-limb muscles contribute to the key markers of ACL loading, namely the anteroposterior tibiofemoral shear force, and the valgus and rotation reaction moments. It was found that the hamstrings and gluteal muscles play a dominant role in protecting the ACL, by opposing the anterior shear force and valgus reaction moment, respectively. These same muscle groups were found to oppose each other in the transverse plane, thus limiting knee rotation loading.

The focus of the third study (Chapter 6) was to determine the contribution of the hamstrings to the medial and lateral tibiofemoral compartment contact force during unanticipated sidestep cutting relative to other lower-limb muscles. This was because ACL

injuries rarely occur in isolation, and are associated with long-term degeneration of articular knee cartilage. A custom musculoskeletal model was created with a modified knee joint mechanism, which permitted the computation of tibiofemoral compartment contact forces via a dynamic equilibrium approach. It was found that medial tibiofemoral contact loading was primarily produced by the vasti, gluteus medius and gluteus maximus and the medial gastrocnemius, whilst lateral tibiofemoral loading was produced primarily by the vasti, soleus, and the medial and lateral gastrocnemius. The medial hamstrings tended to load both compartments, whilst the biceps femoris long head loaded the lateral compartment and induced a relatively small decompression impulse in the medial compartment. Additionally, it was found that most muscles tended to compress both compartments, whilst other muscles had the ability to compress one compartment and decompress the other.

The focus of the fourth study (Chapter 7) was to determine how the hamstrings contribute to coordinating the stance phase of an unanticipated sidestep cut. A musculoskeletal modelling approach was used to estimate lower-limb muscle forces, and a ground reaction force (GRF) decomposition method was used to determine how muscles contributed to the GRFs. It was found that bodyweight support is primarily modulated by the vasti, gluteus maximus, soleus, and gastrocnemius. These same muscles, along with the hamstrings, were also the primary modulators of anteroposterior progression. By contributing to the medial GRF, the vasti, gluteus maximus and gluteus medius were primarily responsible for redirecting the centre-of-mass toward the cutting direction.

This program of research has identified the contribution of the hamstrings, as well as other lower-limb muscles, to knee joint loading and performance during a change-of-direction task. The first study synthesised the retrospective evidence base investigating hamstring strength and flexibility in participants with a history of HSI. This study also identified that assessments of function post HSI tend to focus mostly on the hamstrings during isolated strength assessments, neglecting other lower-limbs muscles. This highlighted the need to better understand the hamstrings role in potentially ACL injurious tasks, relative to other lower-limb muscles. In these investigations the hamstrings were found to be an important muscle group to oppose anterior shear forces during unanticipated sidestep cutting, whilst other non-knee-spanning muscles were found to have a substantial role in developing and opposing other surrogate markers of ACL loading. Similarly, both knee-spanning and non-knee-spanning muscles were found to play a substantial role in compressive loading of the medial and lateral tibiofemoral compartments. Additionally this program of research developed a greater understanding of the contribution of the hamstrings, and other lower-limb muscles, to the

coordination of a sidestep cut. The hamstrings played a key role in maintaining anterior propulsion during early stance, although the majority of the demands of sidestep cutting (bodyweight support, propulsion and redirection) were provided by the vasti, gluteus maximus, soleus and gastrocnemius.

The data from this program of research will inform ACL injury rehabilitation and injury prevention practices which should consider not only targeting the hamstrings but also other non-knee-spanning muscles for loading and unloading the knee during sidestep cutting. Additionally, this thesis provides data that may inform strategies aiming to modulate muscle forces to alter tibiofemoral compressive forces, which may be involved in ACL injury and concomitant meniscal and articular cartilage injury. Finally, this thesis provides further data informing how these muscles contribute to the performance of sidestep cut, in order to achieve optimal balance between performance and injury risk considerations. The findings from this thesis also dictates that future investigations that aim to examine the link between prior HSI and increased knee joint loading need to broaden the scope of such work to consider the influence of other lower-limb muscles as well as multi-planar movements.

List of abbreviations and nomenclature

ACL	anterior cruciate ligament
ADD	hip adductors (adductors brevis, longus and magnus)
ADDBREV	adductor brevis
ADDLONG	adductor longus
ADDMAG	adductor magnus
BFLH	biceps femoris long head
BFSH	biceps femoris short head
cm	centimetres
DOF	degree of freedom
DORSI	ankle dorsi-flexors
EMG	electromyography
fH:Q	function hamstring to quadriceps strength ratio
GAS	gastrocnemius
GASLAT	lateral gastrocnemius
GASMED	medial gastrocnemius
GMAX	gluteus maximus
GMED	gluteus medius
GMIN	gluteus minimus
GRF	ground reaction force
H:Q	hamstring to quadriceps strength ratio
HAM	biarticular hamstrings
HSI	hamstring strain injury
ICC	intraclass correlation coefficient
ID	inverse dynamics
IK	inverse kinematics
IQR	interquartile range
I^2	percentage of variation across studies due to heterogeneity rather than chance
kg	kilograms of body mass
m	metres
MEDHAM	medial hamstrings
ms	milliseconds
N	newtons of force

Nm	newton metres of torque
Nm/kg	newton metres of torque normalised to body mass
nRMSE	normalised root mean square error
Ns	newton seconds of impulse
PATS	progressive agility and trunk stabilisation rehabilitation protocol
PIRI	piriformis
PRES	progressive running and eccentric strengthening rehabilitation protocol
RECFEM	rectus femoris
REML	restricted maximum likelihood
RRA	residual reduction algorithm
SD	standard deviation
SEMIM	semimembranosus
SEMIT	semitendinosus
SENIAM	Surface Electromyography for the Non-Invasive Assessment of Muscle
SOLEUS	soleus
VASINT	vastus intermedius
VASLAT	vastus lateralis
VASMED	vastus medialis
VASTI	vastus intermedius, lateralis and medialis
W	watts of power
95% CI	95 percent confidence interval

Chapter 1 – Introduction and overview

Anterior cruciate ligament (ACL) injuries are one of the most common knee injuries sustained during athletic participation (1). Moreover, ACL injuries are associated with substantial convalescence and rehabilitation times (2), and associated financial costs (3, 4). Considering these points and that ACL injury is also associated with an increased risk of early onset knee osteoarthritis (5-7), the development of effective strategies for ACL injury prevention and rehabilitation are of paramount importance (8).

Research analysing video footage of ACL injuries has found the common mechanism to be non-contact dynamic tasks, such as single-leg landings, sudden decelerations and rapid change-of-direction manoeuvres (9-15). In particular, ACL injury tends to occur promptly after initial contact (10), where the knee joint experiences relatively large degrees of knee valgus and rotation (either internal or external) and high mechanical loads (10-15). Although video-based observations have limited accuracy (16), these findings are consistent with cadaveric studies showing that frontal and transverse plane knee mechanics influence ACL loading (17-20).

Whilst the primary role of the ACL is to resist anterior translation of the tibia relative to the femur (21), both cadaveric and modelling studies have shown that frontal and transverse plane knee mechanics can also influence ACL loading (17-20). In the frontal plane, a greater externally applied knee valgus or varus moment both have the potential to increase load on the ACL (17, 20). However, knee valgus position has been reported to be the more common mechanism of injury in video-based analyses (9, 10, 15). In the transverse plane, an externally applied internal rotation moment of the tibia with respect to the femur has been found to expose the ACL to higher loads than an externally applied external rotation moment of the tibia with respect to the femur (17, 20). Moreover, non-sagittal plane knee joint moments have been shown to have the greatest influence on ACL loading when they occur simultaneously, and especially in conjunction with an anterior shear force (17, 19, 20, 22). As the primary role of the ACL is to resist anterior translation of the tibia relative to the femur (21), it is unsurprising that anterior and posterior shear forces have been consistently shown to load and unload the ACL, respectively (17-19, 23-26). As a consequence of this research, the anterior shear, knee valgus and knee internal rotation loading patterns are often considered surrogate markers for ACL loading. Therefore, with a better understanding as to how these critical knee joint loads

are developed, it may be possible to improve preventative measures and rehabilitative strategies for ACL injuries.

Muscles produce forces that can cause and oppose these critical knee joint loads, and therefore play an important role in dictating the size and the nature of the loads experienced by the ACL. For example, the quadriceps have been shown to generate an anterior tibiofemoral shear force which is directly opposed by the ACL (27). In contrast, the hamstrings have the potential to mitigate anterior tibiofemoral shear forces, thereby reducing the amount of anterior tibial restraining force needed from the ACL (27, 28). Unsurprisingly, lower hamstring strength has been associated with increased risk of subsequent ACL injury (29), presumably due to a lesser ability to provide posterior tibiofemoral shear force. Subsequently, "appropriate" function of the hamstrings has been considered important for mitigating ACL injury risk. For example, ACL-injury preventative strategies often aim to increase hamstring strength, or increase hamstring activation during potentially injurious manoeuvres (30-32). Additionally, prior hamstring strain injury (HSI) has been hypothetically proposed to increase the risk of ACL injury (33), due to chronic neuromuscular deficits present in previously strained hamstrings (34-37).

Despite the amount of research demonstrating the importance of the hamstring group for unloading the ACL, further work is still needed. The importance of the hamstring group is based largely on its anatomical line of action in the sagittal plane (i.e. it induces a posterior shear force at the tibia). However, ACL loading is multi-planar, thus non-sagittal plane anatomical classifications also require consideration for the hamstrings and other muscles. Whilst the anatomical orientation of a muscle influences its induced actions, it does not fully explain their action. Through "dynamic coupling", any muscle in the body can induce an acceleration of any segment in the body (38). Importantly, this means that knee joint reaction forces and moments can be induced by muscles which do not span the knee. In addition to this, the way in which a muscle induces segment accelerations and joint reaction forces is dependent on the orientation of all segments in the system (38). Therefore, studies investigating muscle contributions to knee loading that have failed to account for whole body kinematics are also limited, as the interpreted function of the muscle of interest (i.e. the induced accelerations and joint loads) can sometimes be counter intuitive to their anatomical classification. Inferring muscle contributions to knee joint loading during potentially injurious manoeuvres which involve multi-planar loading, such as sidestep cutting, is therefore needed. More complete knowledge of how the hamstrings contribute to knee joint shear, valgus and rotational loading during sidestep cutting relative to other lower-limb muscles would better inform preventative

interventions aiming to reduce ACL injury risk, which often aim to increase the strength or activation of specific muscle groups (30-32, 39-43). Additionally, since ACL injuries rarely occur in isolation and often involve damage to other tissues in the knee joint, leading to an increased risk of knee osteoarthritis (44, 45), it is important to consider how lower-limb muscles contribute to compressive knee loading. This data could allow interventions to not only modulate ACL injury risk, but also influence surrounding structures such as articular cartilage and menisci. Furthermore, since manoeuvres such as sidestep cutting are required in many sports, it is important to understand how the hamstrings contribute to the coordination of a sidestep cut, in order to optimise the performance and risk-mitigating outcomes from risk reducing interventions.

Defining muscular coordination or function of a sidestep cut can be achieved in multiple ways. Neptune and colleagues (46) used surface electromyographic (EMG) data to understand the magnitude and timing of activation of key muscles during cutting manoeuvres. Surface EMG, however, is limited to muscles that are large and superficial. Additionally, inferring muscle action during complex movements cannot be achieved with EMG data alone. As previously discussed, muscle contributions to segment accelerations can be difficult to predict and are sometimes counter intuitive to their anatomical definition, thus additional analysis such as dynamic simulation is needed to investigate how muscles coordinate a movement. Several studies have used musculoskeletal simulation to determine muscle function and coordination during walking (47-52) and running (53, 54) by determining each muscle's contribution to the ground reaction force. No studies, however, have investigated sidestep cutting. Thus complete knowledge of important lower-limb muscles for the coordination and performance of a sidestep cut is currently lacking. Subsequently, it is not known if interventions aiming to alter muscle activation/function (to reduce injury risk) may have deleterious effects on performance.

Given these gaps in the literature, the aim of this program of research was to determine the role of individual muscles in the development of knee joint loading to better understand the importance of the hamstrings to knee joint loading. The specific aims of each study were to 1) determine the impact of prior HSI on lower-limb function, 2) determine how the hamstrings contribute to three-dimensional loading of the knee joint during a potentially injurious manoeuvre relative to other lower-limb muscles, 3) determine how the hamstrings contribute to medial and lateral tibiofemoral compressive loading relative to other lower-limb muscles and 4) determine how individual muscles contribute to the coordination of a sidestep cut. A thorough review of the current literature related to muscle force and ACL loading can be found in Chapter 2, an overview of methodology can be found in Chapter 3, after which Chapters 4,

5, 6 and 7 contain the original research which address the aims of the thesis. The findings, implications and limitations from all studies are then discussed in Chapter 8.

Chapter 2 – Literature review

Publication statement:

This chapter is comprised of the following paper currently under review at *Sports Medicine*:

Maniar, N, Cole, M.H, Bryant, A.L, & Opar, D.A. Muscle force contributions to anterior cruciate ligament loading. *Sports Medicine*. In review.

2.1 Abstract

Anterior cruciate ligament (ACL) injuries are one of the most common knee injuries sustained during athletic participation. Moreover, ACL injuries are associated with long convalescence periods, extensive long term debilitation and associated financial burden. Subsequently, prevention of ACL injuries is of paramount importance. Numerous interventions have been developed to reduce injury risk, many of which aim to alter the strength and/or activation of key muscle groups thought to influence loading of the ACL. Knowledge of how individual muscles can contribute to ACL loading is therefore critical to inform these interventions. However, the relationship between muscle forces and ACL loading has been investigated by numerous different studies, often with differing methods and conclusions. Subsequently, this review aims to synthesise the evidence pertaining to the relationship between muscle force and ACL loading. Consistent evidence was found for the quadriceps and the hamstrings, showing that they tended to load and unload the ACL, respectively. These effects, however, were mediated by the knee flexion angle. The gastrocnemius and soleus were also found to load and unload the ACL, respectively, although this evidence was less extensive than that of the quadriceps and hamstrings. Very little evidence was found for other muscle groups. Future research is needed to elucidate the role of muscle force on ACL loading for many other muscles, especially during high-demand sporting manoeuvres.

2.2 Introduction

Anterior cruciate ligament (ACL) injuries are one of the most common knee injuries sustained during athletic participation (1), with incidence rates reported to be 0.05 and 0.08 per 1000 exposures for males and females, respectively (55). These injuries are particularly prevalent in sports that require frequent changes of direction, such as basketball, soccer, football and hockey (55) and are associated with substantial convalescence and rehabilitation time (2), and associated financial costs (3, 4). Importantly, current data suggest that approximately 30% of athletes who suffer an ACL injury will experience a recurrence within 24 months of returning to sport (56). Moreover, ACL injury, treated conservatively or surgically, has also been associated with an increased risk of early onset knee osteoarthritis (5-7); thus, development of effective strategies for ACL injury prevention are of paramount importance (8).

Over the years, many programs aiming to reduce the incidence of ACL injuries have been developed (30-32, 39-43, 57-63). These programs typically emphasise multiple neuromuscular components, including those related to technique modification, muscle activation patterns, strength, explosiveness, balance, agility and flexibility. A recent systematic review and meta-analysis found that these multi-component programs are effective at reducing injury risk (64), but the authors were unable to determine which specific training components were most important to minimising injury risk. Determining which specific neuromuscular components to target is needed to develop optimal interventions that prioritise the mitigation of risk factors. Current interventions incorporate components that are chosen based predominately on known risk factors for ACL injury, loading mechanisms, and sound clinical reasoning (30-32, 39-43, 57-63).

Although risk factors for ACL injury have been accumulated over the years (65-68), they are often difficult to study due to the relatively low incidence of ACL injury (55). ACL injury and loading mechanisms are derived from video analysis of injury scenarios (9-15), biomechanical and simulation studies (69-71), as well as cadaveric models (19, 72-74). These studies have identified key knee joint loading parameters that have been associated with ACL injury risk (75) and these parameters have been used as surrogates for ACL loading in biomechanical studies (69). Importantly, muscles produce forces that can cause and oppose these key knee joint loads and therefore, play a critical role in dictating the size and the nature of the loads experienced by the ACL. Various isolated studies have used differing methods to determine the role of individual muscles on ACL loading. Knowledge of how muscles contribute to ACL loading is essential to inform preventative interventions that often target the strength and/or activation of specific muscle groups in order to unload the ACL (30-32, 39-

43). Therefore, the purpose of this narrative review was to synthesise the existing evidence to determine how specific lower-limb muscles contribute to ACL force/strain. The specific aims of this review include:

1. Provide a brief primer on knee joint biomechanics
2. Describe the injury and loading mechanisms of the ACL
3. Provide an overview of methodological considerations for studies that investigate the role between muscle force and ACL loading
4. Synthesize the current evidence pertaining to the relationship between lower-limb muscle force and ACL loading
5. Provide potential clinical implications and recommendations for future research

2.3 Knee joint biomechanics

Although motion at the knee can occur in 6 degrees of freedom, these can be described about 3 principal axes (Figure 2-1). The superior-inferior axis (y-axis) is parallel to the shaft of the tibia; whilst the anteroposterior (x-axis) and mediolateral (z-axis) axes are perpendicular to the y-axis and are orthogonal to each other. The three associated planes are defined as the sagittal (xy), frontal (yz) and transverse (xz) planes. Translation along the y-axis is described as superior (or proximal) and inferior (or distal). Since these are expressed relative to the tibia, a superiorly-directed force is compressive to the knee joint, whilst and inferiorly directed force induces decompression (or distraction). Translation along the x-axis is described as anterior and posterior, whilst the z-axis allows lateral and medial translations. Knee flexion and extension occurs about the z-axis, with full knee extension defined as 0 degrees. Knee varus (adduction) and valgus (abduction) rotation occurs about the x-axis. Knee valgus rotation occurs when the distal aspect of the tibial moves away from the midline of the body, in the frontal plane. Knee internal and external rotation occurs about the y-axis. Knee internal rotation occurs when the anterior surface of the tibia rotates towards the midline of the body, in the transverse plane. For the present review, we describe forces and moments along and about these axes based on the movements they induce on the tibia. For example, a valgus moment induces valgus rotation of the tibia relative to the femur, and an anterior shear force induces anterior translation of the tibia relative to the femur.

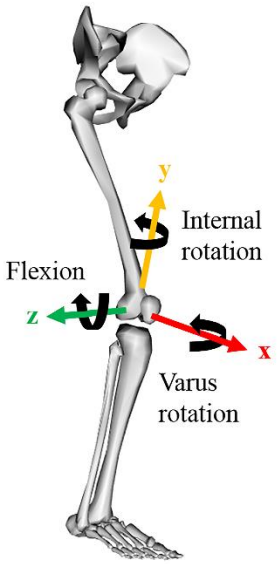

Figure 2-1. Knee joint axis definitions used in the present review. Note the lower-limb model used (76) was visualised in OpenSim v3.3 (77).

2.4 Injury and loading mechanisms of the ACL

Research analysing sports-related video/television footage of ACL injuries has found the common mechanism of ACL injury to be non-contact dynamic tasks, such as single-leg landings, sudden decelerations and rapid change-of-direction manoeuvres (9-15). In particular, ACL injury tends to occur shortly after initial contact (10), where the knee joint experiences relatively large degrees of knee valgus and rotation (either internal or external) and high mechanical loads (10-15). Although video-based observations have limited accuracy (16), these findings are consistent with cadaveric studies showing that frontal and transverse plane knee mechanics influence ACL loading (17-20).

In the frontal plane, higher knee valgus or varus moments both have the potential to increase loads on the ACL (17, 20). However, knee valgus collapse has been reported to be the more common mechanism of injury in video-based analyses (9, 10, 15). In the transverse plane, an internal rotation moment of the tibia with respect to the femur has been found to expose the ACL to higher loads than an external rotation moment of the tibia with respect to the femur (17, 20). Moreover, non-sagittal plane knee joint moments have been shown to have the greatest influence on ACL loading when they occur simultaneously, and especially in conjunction with an anterior shear force (17, 19, 20, 22). As the primary role of the ACL is to resist anterior translation of the tibia relative to the femur (21), it is unsurprising that anterior and posterior shear forces have been consistently shown to load and unload the ACL, respectively (17-19, 23-26). Knee joint compression is also thought to play a role in ACL

injury. Early work suggested that increases in joint compression would be favourable due to decreased tibial translation (78), however more recent work has shown that compression may increase strain on the ACL (79-81).

As a consequence of this research, anterior translation, knee valgus and knee internal rotation (or the forces and moments that produce these) are often considered surrogate markers for ACL loading. Therefore, understanding how muscles contribute to or oppose these critical knee joint loads may provide insight into how these muscles load and unload the ACL.

2.5 Search strategy

A retrospective, citation-based methodology (82) was used to obtain articles from databases such as PubMed and Google Scholar. Search terms included those related to the ACL ("anterior cruciate ligament", "ACL", "knee") as well as muscle, ligament or joint loading ("strain", "force", "shear", "translation", "rotation", "valgus", "abduction" "muscle force", "muscle contributions", "muscle induced"). Only peer-reviewed literature in English were considered. In this review, we only included articles which specifically determined the role of lower-limb muscle forces on ACL force/strain, or any other of the previously described surrogate markers of ACL loading.

2.6 Methodological considerations

To assess how muscle force may contribute to ACL loading, studies have used in-vitro, in-silico and in-vivo methods. Each of these methods is associated with distinct advantages and limitations. Hence, prior to synthesis of relevant findings, the methods used in these studies must first be scrutinised. Note that a summary of these studies is provided in Appendix II Table 1.

2.6.1 In-vitro

Numerous studies have adopted an in-vitro approach to investigate the relationship between muscle force and ACL loading (18, 27, 28, 83-98). Via robotic manipulation of cadaveric knees, these studies can alter joint angles of cadaveric knees to simulate a variety of knee angles (27, 86, 87, 91) and high-impact landings (84, 85). Muscle forces can be simulated via cables or springs attached at the site of the muscle of interest. However, these cables often apply static forces (27, 84, 85, 87, 91) that are not representative of in-vivo conditions. Additionally, since only the knee is evaluated, these methods cannot account for full-body kinematics and the influence of the many non-knee-spanning muscles that can produce knee joint loads via dynamic coupling (38). However, unlike in-vivo approaches, in-vitro investigations can load

tissues to the point of failure (74); thus, actual injury thresholds can be determined as long as the cadaveric tissues are appropriately preserved. Nevertheless, data pertaining to ACL injury thresholds and failure loads should be interpreted with consideration of the characteristics of the cadavers, as tissue properties differ with aspects such as age (99) and gender (100).

2.6.2 In-silico

In-silico refers to the use of computer simulation techniques. In the context of muscle forces and ACL loading, this involves employing musculoskeletal modelling (101-108) and/or finite element modelling (105, 109, 110) techniques. The use of these techniques offers several distinct advantages. Firstly, modelling enables the investigation of cause-effect research questions that are otherwise impractical or impossible to directly assess (77). For example, using an in-silico approach, it is possible to assess the relationship between muscle force and joint loading during dynamic tasks such as walking (107, 111, 112). Additionally, musculoskeletal modelling can overcome some limitations of cadaveric approaches, whereby interactions between muscular forces and whole body skeletal dynamics can be accounted for (38). As such, the contribution of both knee-spanning and non-knee-spanning muscles to knee joint loading can be assessed by determining muscular contributions to ground reaction forces (GRF) (107, 112). However, validation of these musculoskeletal simulations poses a fundamental challenge for the research community, as it is generally based on numerous assumptions (113). For example, muscle forces can be estimated via a variety of EMG-driven (114) and optimisation (115-117) approaches, but since muscle forces are not practically feasible to measure in-vivo, direct validation of muscle forces is not possible. However, best practice recommendations for validation and verification of musculoskeletal simulations are available (113). For example, indirect validation of muscle forces is possible via comparison of the estimated and experimentally-measured joint contact forces (e.g. in participants with instrumented knee implants), due to the high dependency of contact loads on muscle forces (118). Subsequently, modelling studies should be interpreted following careful consideration of the validation and verification procedures.

2.6.3 In-vivo

In-vivo assessments of muscle force contributions to ACL loading can be conducted via invasive and non-invasive protocols; however, these studies are often isolated to single cases. ACL strain can be calculated directly via surgical placement of a differential variable reluctance transducer on the ACL fibres, with electrical stimulation of muscles to assess the relationship between muscle force and ACL strain (119). The primary advantage of this

approach is direct measurement of ACL strain in-vivo, along with controlled stimulation of muscles. However, this method is highly invasive and participants require general anaesthesia. Moreover, only sub-injurious isolated muscle forces can be assessed, and not during clinically-relevant high-demand sporting manoeuvres (e.g. sidestep cutting and single-leg landing). The way in which a muscle contributes to joint loading is dependent on the orientation of all segments in the system (38); thus, failing to account for whole body kinematics during high-demand tasks sporting manoeuvres limits the findings from these methods.

Non-invasive in-vivo methods are possible, although they require indirect methods for quantifying ACL strain and/or muscle force contribution. A series of studies (120-123) have used surface or, more invasively, intramuscular electromyography (EMG) to indirectly assess the contribution of particular muscles to ACL loading. Serpell and colleagues (122) coupled EMG analysis with fluoroscopy to assess tibiofemoral skeletal movement during a single-leg step-up and tracked ACL attachment sites in order to estimate ACL strain. Other studies incorporated frontal plane knee moments derived via a dynamometer (120, 121) or inverse dynamics (123) as a surrogate marker of ACL loading during isometric action. The major limitation of these studies was that the muscle force was not controlled and, clearly, none of the experiments performed their assessments during high-demand sporting manoeuvres. However, EMG data can be processed to obtain in-silico estimates of muscle force (106, 114), and the highly accurate fluoroscopy technique (124, 125) has been used to track tibiofemoral kinematics during drop landings (126). These methods therefore warrant further research. One study (97) used a KT-1000 arthrometer to monitor anterior tibial translation in response to different passive muscle forces from the ankle plantar-flexors. These muscle forces, however, were not directly monitored since force was altered indirectly by changing the ankle dorsi-flexion angle.

2.7 The role of muscles in ACL loading

Despite the aforementioned limitations of each method, it is noted that many of the limitations inherent to each method are often complemented by the strengths of alternate methods. As such, should relatively consistent findings be reported using different techniques across studies, this would provide some confidence in the validity of each method. The following section synthesises findings from studies using various methodologies in an effort to describe the role of different lower-limb muscles in ACL loading.

2.7.1 Quadriceps

The quadriceps are one of the most heavily investigated muscle groups in relation to ACL loading (27, 84-88, 90-92, 95, 103, 104, 107-110, 127) and studies have consistently shown that the force produced by this muscle group significantly contributes to the loads placed on this structure. For example, Withrow and colleagues (84) showed that the ACL strain during simulated impact landings had a strong positive correlation (R^2 = 0.74) with the change in quadriceps tendon force. However, the influence of quadriceps force appears to be dependent on the knee flexion angle. At lower knee flexion angles (i.e., less than ~30-50 degrees), quadriceps/vasti force has been shown to induce ACL loading (87, 90, 91, 93-95, 103, 110), anterior shear force (108), anterior tibial translation (27, 92, 96, 98), knee valgus rotation (92, 96), a knee valgus moment (107, 108), and tibial internal rotation (27, 92, 96, 98). However, at very high knee flexion angles (i.e., greater than ~80 degrees), the quadriceps have a limited role in ACL loading and may even serve to unload this structure (87, 90, 95, 103) due to the changing angle between the patella tendon and the longitudinal axis of the tibia at increased knee flexion angles (98, 104).

2.7.2 Hamstrings

The hamstrings have received substantial attention in the literature given their potential to unload the ACL (27, 28, 85-89, 91, 94, 101-104, 109, 122, 127-129). This is primarily due to the hamstrings ability to produce a posterior shear force at the tibia (86, 108, 129). Hence, the majority of studies have looked at the role of hamstring-quadriceps co-contraction to assess whether the hamstrings can reduce the injurious loads imposed by the quadriceps muscle group (27, 28, 85, 86, 91, 94, 104, 122, 128). These studies have consistently reported that hamstring co-contraction can have a protective effect by reducing ACL strains and forces (85, 91, 94, 109, 127), anterior shear forces (86, 128, 129), anterior tibial translation (27, 28, 86), and internal tibial rotation (27, 28, 86). Like the quadriceps, the effectiveness of hamstring contraction at influencing ACL loading is dependent on the knee flexion angle. Near full extension, the hamstrings are relatively ineffective at producing a posterior shear force due to their line of action and small mechanical advantage in this position (127). At knee flexion angles of greater than or equal to ~20-30 degrees, the hamstrings are more effective at producing posterior shear forces, thus unloading the ACL (27, 28, 86, 87, 90, 91, 127). Additionally, computational modelling studies have demonstrated that hamstring muscle force reduces the estimated ACL loads during single-leg drop landing (101) and sidestep cutting tasks (102). In the frontal plane, hamstring force has also been shown to oppose valgus loading

during early stance in walking (107), whilst EMG data also suggest that hamstring and quadriceps co-contraction may also play a role in limiting valgus and varus loading at the knee (106).

Each hamstring muscle has a different influence on ACL loading, owing to their different orientations and moment arms relative to the knee joint (130). Two studies (89, 129) have shown that the biceps femoris group has the greatest ability to unload the ACL given its ability to oppose internal rotation of the knee (89) and its relatively large capacity to generate muscle force (129) and produce adequately-sized posterior shear forces (89, 129). Compared with the biceps femoris, the orientation of the semimembranosus limits its ability to oppose ACL loading, whilst the semitendinosus is heavily limited by its relatively small physiological cross-sectional area (129-131). In contrast to these findings, Serpell and colleagues (122) suggested that higher medial to lateral hamstring EMG activation patterns are needed to unload the ACL during a step-up task. Whilst muscle force was not directly quantified or controlled in this study, additional research is needed to further elucidate the role of the individual hamstring muscles.

2.7.3 Gastrocnemius

The role of the gastrocnemius in ACL loading is somewhat contentious (83, 88, 97, 101, 105, 108, 119-121, 123, 127). Both simulation (105) and in-vitro (83) studies have shown that gastrocnemius muscle force acts as an ACL-antagonist across majority of the knee flexion range by inducing increased ACL force and anterior tibial translation, respectively. Moreover, simulation studies have also shown that the gastrocnemius acts as an ACL antagonist during single-leg landings (101), and produces anterior shear force (108) and knee valgus loading during gait (107, 108). An in-vivo approach from Fleming and colleagues (119) supported these findings, with direct electrical stimulation of the gastrocnemius shown to induce ACL strain at knee flexion angles of 15 and 30 degrees.

Despite these consistent findings, Durselen and colleagues (88) reported that gastrocnemius force did not contribute to ACL strain at knee flexion angles of 0 to 110 degrees. However, these findings may be explained by the low applied muscle forces (gastrocnemius forces = ~40-50N). Whilst these forces are much lower than what would be expected in-vivo, the authors reported that low muscle forces were needed to avoid cadaveric tissue failure. EMG data suggests that the medial gastrocnemius tends to oppose knee valgus and internal rotation loading, whilst the lateral gastrocnemius plays the opposite role (120, 121, 123). Whilst this may suggest that the gastrocnemius protect the ACL by limiting frontal and transverse plane

loading, conclusions regarding the net effect on ACL loading cannot be made since direct ACL strain and anteroposterior shear loading were not considered in these studies. Sherbondy and colleagues (97) found that passively dorsi-flexing the ankle resulted in reduced anterior tibial translation measured using a KT-1000 arthrometer, concluding that the ankle plantar-flexors play a role in stabilizing the knee against anterior tibial translation. However, these authors replicated this test in cadavers in the same study (97) and found that the influence of ankle dorsi-flexion on tibial translation persisted when the gastrocnemius was cut, but not when the soleus was cut, suggesting the observed effect was more likely due to the soleus.

2.7.4 Soleus

In addition to the observations from Sherbondy and colleagues (97), two other studies have also suggested the soleus may oppose ACL loading. Using a computational musculoskeletal model, Mokhterazedah and colleagues (101) showed that the soleus opposes ACL loading during drop landing by producing a posterior shear force at the tibia. In an in-vitro study (83), investigators dissected apart the soleus from the gastrocnemius in cadavers, and demonstrated that soleus muscle force caused posterior translation of the tibia, particularly at 50 degrees of knee flexion. However, soleus muscle forces during walking have been shown to induce knee valgus loading during late stance, via their contribution to the GRF (107). Thus, the specific role of the soleus in ACL loading remains largely unclear and further consideration of how this muscle contributes to multi-planar loading at the knee is needed.

2.7.5 Other muscles

Despite limited research, other muscles may also influence knee joint loads. In particular, the gluteal muscle group (especially the gluteus medius) has been noted as a potentially important contributor to the prevention of dynamic knee valgus collapse, via its role in producing hip abduction (132). This hypothesis is somewhat supported by a prospective study that demonstrated increased risk of ACL-injury in association with lower hip abduction strength (133). However, direct investigation of gluteal muscle force and knee joint loading is limited. Indeed, only one study (107) has investigated muscular contributions to the knee varus moment during walking. These authors found that the gluteus medius and maximus were major contributors to the knee varus moment via their contribution to the GRF, thus demonstrating the potential of these muscle to oppose knee valgus loading. However, due to vastly different biomechanical demands between walking and high-demand sporting manoeuvres, it remains unclear whether the role of the gluteal group is the same during these tasks (38).

EMG data have also suggested that the tensor fascia latae and sartorius muscles may induce knee valgus loading, whilst the gracilis tends to oppose this (120, 121). However, these studies were based on isometric contractions, which may limit their applicability to dynamic injury mechanisms. Additionally, these muscles have a relatively small physiological cross-sectional area (131, 134), suggesting actual force (and therefore valgus/varus torque) production may be limited. Further research is required to confirm the roles of these muscles during dynamic movement and to determine whether the magnitudes of frontal plane loading produced are of practical relevance.

2.8 Clinical considerations

Changing the strength and/or activation of certain muscle groups remains an important component of ACL injury preventative strategies (30-32, 39-43); thus, understanding how individual muscles contribute to ACL loading is necessary to inform these interventions. Findings of the present review suggest that the quadriceps and gastrocnemius muscles are ACL antagonists and their contraction increases ACL load. By contrast, the hamstrings and soleus muscles are ACL agonists and these muscles have the capacity to reduce ACL loads.

2.8.1 Anterior cruciate ligament agonists

Evidence presented in this review supports targeting the hamstrings as an important component of ACL injury preventative programs (30-32). Based on the importance of the hamstring muscle group for unloading the ACL, any pathology which may influence force production or activation of the hamstrings, such as prior hamstring strain (35, 36, 135, 136) or ACL reconstruction involving the use of a semitendinosus graft (137-140), should also be considered as potentially influencing factors that may need to be considered by clinicians. As such, when developing preventative strategies or interventions, consideration should be given to the fact that although the hamstrings appear to be highly responsive to strengthening exercises (141, 142), their adaptability may be limited by the presence of prior hamstring pathology (143, 144).

Many current strengthening programs have also targeted and/or monitored the gluteal group (32, 39, 40), despite a lack of evidence that this muscle group has the capacity to unload the ACL during high-demand sporting manoeuvres. However, increasing evidence suggests that hip muscle weakness or asymmetries are associated with ACL injuries (133, 138). Future research should investigate the role of the gluteal and other non-knee-spanning muscle groups, as these have been largely under researched. Additionally, future studies should investigate the role of these muscles in high-demand sporting manoeuvres, such as sidestep cutting and single-leg landing, in order to account for whole body dynamic coupling (38). Information from future

research could improve current exercise interventions, and may also be used to inform return to play criteria following ACL reconstruction (138, 145). For example, identifying that other non-knee-spanning muscles are important for unloading the ACL may lead to the inclusion of strength tests for these muscle groups in clinical decision making.

2.8.2 Anterior cruciate ligament antagonists

Whilst the quadriceps and gastrocnemius are considered ACL antagonists, interventions aiming at altering their force production during dynamic movements require additional considerations. For example, EMG and/or musculoskeletal modelling studies have shown that high-demand sporting manoeuvres, such as single-leg landings, are associated with high activations and/or forces of the quadriceps and gastrocnemius muscle groups (46, 101, 146, 147). These data suggest that these muscles play a critical role in the performance of these manoeuvres, potentially via their contribution to bodyweight support as they do in walking (47-52) and running (148, 149). Additionally, these muscle groups play a critical role in tibiofemoral joint compression during gait (107, 111, 112), which may be necessary to offset cartilage degeneration in the years following ACL injury (150). Subsequently, interventions that aim to reduce ACL injury risk by reducing the muscle force contributions from the quadriceps or gastrocnemius may have unwanted consequences. It is therefore recommended that further research seek to elucidate the role of these muscles in relation to tibiofemoral compressive loading and performance during potentially injurious manoeuvres, such as sidestep cutting and single-leg landing.

2.9 Conclusion

In summary, this review highlights that the quadriceps, hamstrings and ankle plantar-flexors have the most evidence as contributors to ACL loading and unloading. In general, the evidence suggests that the quadriceps and hamstrings are the primary antagonists and agonists of the ACL, respectively. Although data is limited, the gastrocnemius and soleus may also be antagonists and agonists of the ACL, respectively. Very limited evidence is available for other muscles; thus, future research is needed to elucidate their potential roles in ACL loading and unloading.

Chapter 3 – Methodology and design

As per university guidelines, the methods utilised within each study of this thesis are described in their entirety below. Subsequently Chapters 4, 5, 6, and 7 contain the specific methods used in each study presented according to guidelines provided by the respective journals.

3.1 Study 1- Hamstring strength and flexibility after hamstring strain injury: a systematic review and meta-analysis

For Chapter 4, it is noted here that no additional methodological description is required. To avoid repetition for the reader, the methodology (described in Chapter 4) will not be repeated here, and the reader is directed to Chapter 4.

3.2 Studies 2-4: Musculoskeletal modelling of unanticipated sidestep cutting

Chapters 5, 6 and 7 describe a series of musculoskeletal modelling experiments to investigate muscle function during unanticipated sidestep cutting. Unanticipated sidestep cutting was chosen as the primary experimental task since it is a commonly reported mechanism of anterior cruciate ligament (ACL) injury (9, 10, 14, 15, 151). Musculoskeletal modelling was chosen as it allows for the estimation of physiological parameters that are otherwise impossible to measure (77). Additionally, musculoskeletal simulation can be conducted in a cause-effect manner. However, care must be taken to ensure that computational simulations are appropriately validated and verified (113). This involves a thorough consideration of experimental data collection procedures and the choice of appropriate computational analysis techniques, which balances model complexity and computational efficiency. Subsequently, the following section describes the experimental data collection and musculoskeletal simulation analysis in more detail than that described in Chapters 5, 6 and 7.

3.2.1 Participants

Eight recreationally active healthy males (age: 27 ± 3.8 years; height: 1.77 ± 0.09m; mass: 77.6 ± 12.8kg) were recruited. This sample size was justified based on prior studies that have conducted similar analysis (e.g. (101, 107)). All participants had no current or previous musculoskeletal injury likely to influence their ability to perform the required tasks. Such injuries included prior hamstring strain injury, ACL injury, or any injury requiring surgical intervention. All participants provided written informed consent to participate in the study. Ethical approval was granted by the Australian Catholic University human research ethics committee (approval number: 2015-11H), and the study was carried out in accordance with the approved guidelines.

3.2.2 Instrumentation

Three-dimensional marker trajectories were collected at 200Hz using a nine camera motion analysis system (VICON, Oxford Metrics Ltd., Oxford, United Kingdom). Ground reaction forces (GRF) were collected via two ground-embedded force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) sampling at 1000Hz. Surface electromyographic (EMG) data were collected at 1000Hz from 10 lower-limb muscles on the dominant leg (defined as the kicking leg; right side for all participants) via two wireless EMG systems (Noraxon, Arizona, USA; Myon, Schwarzenberg, Switzerland). Two EMG systems were required as each system had only eight channels. The time delay for each system was accounted for, thus synchronising signals from each EMG system with the motion and force plate data.

3.4.3 Procedures

All participants were barefoot during the completion of all tasks. Although sidestep cutting is typically performed in footwear, barefoot conditions allowed exposure of the foot for marker placement and kept the foot-ground interaction consistent across all participants. The skin was prepared for surface EMG collection by shaving, abrasion and sterilisation. Circular bipolar pre-gelled Ag/AgCl electrodes (inter-electrode distance of 2cm) were then placed on the vastus lateralis and medialis, rectus femoris, biceps femoris, medial hamstrings, medial and lateral gastrocnemius, soleus, tibialis anterior and peroneus longus muscles in accordance with Surface Electromyography for the Non-Invasive Assessment of Muscle (SENIAM) guidelines (152). EMG-time traces during forceful isometric contractions were visually inspected to verify the correct placement of the electrodes and to inspect for cross-talk. Forty-three 14 mm retroreflective markers were affixed to various anatomical locations (Figure 3-1) on the torso (sternum, the spinous process of the 7^{th} cervical vertebra, the spinous process of a mid-thoracic vertebra, the tip of each acromion), pelvis (anterior and posterior superior iliac spines), upper-limbs (medial and lateral elbow and distal radius and ulna) and lower-limbs (medial and lateral femoral epicondyles, medial and lateral malleoli, first and fifth metatarsophalangeal joints, calcaneus and three additional markers on each shank and thigh) of each participant.

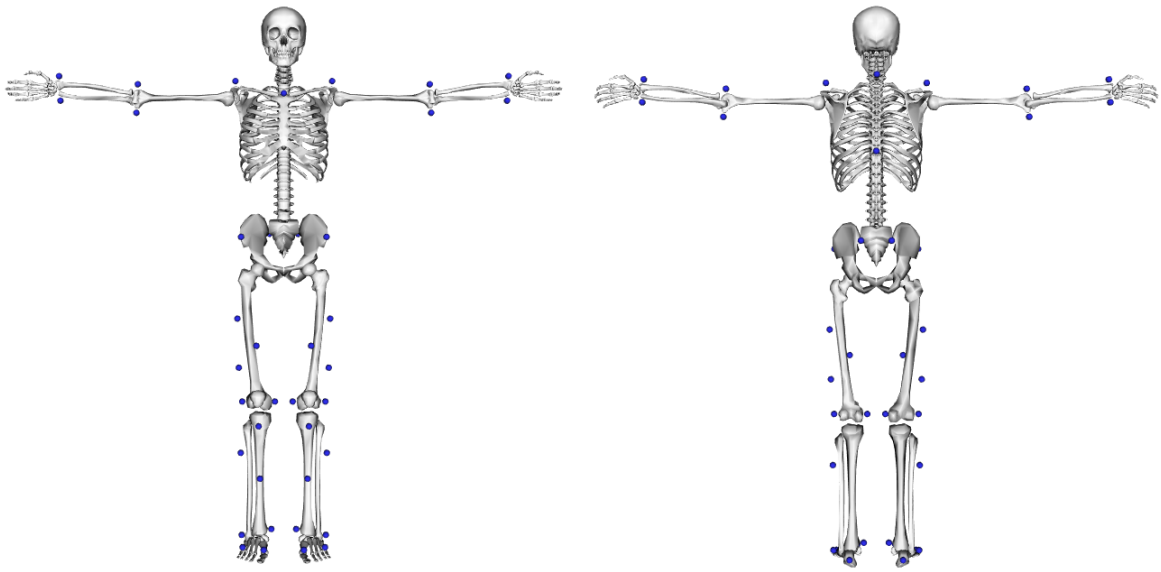

Figure 3-1. Anterior and posterior view of the experimental marker setup for data collection.

Each participant completed two unanticipated change-of-direction tasks on their dominant leg. Participants were required to perform two single-leg hops for a standardised distance of 1.35m, and then as quickly as possible cut to the left (45º sidestep cut) or to the right (45º crossover cut) upon landing from the second hop (Figure 3-2). We used a hopping approach based on prior research (153) because it allows speed and foot placement on the force plate to be well controlled across participants relative to a running approach. The direction of cut was randomly dictated by a set of timing gates (Smartspeed, Fusion Sport, Australia) that delivered a light signal ~450ms prior to initial contact on the force plates. Floor markings were used to indicate the starting point, the hop landing targets and the required 45º angle from the force plates for the cutting direction. A successful trial required that the participant completed the task correctly with the entire foot landing within the force plate. This protocol produced approach velocities (2.24 ± 0.15 m/s) and cutting angles (41 ± 2º) that were consistent with characteristics reported during ACL injuries (151). Note that we only analysed sidestep cuts in this investigation, as this task has been most commonly associated with injury to the ACL (9, 10, 14, 151).

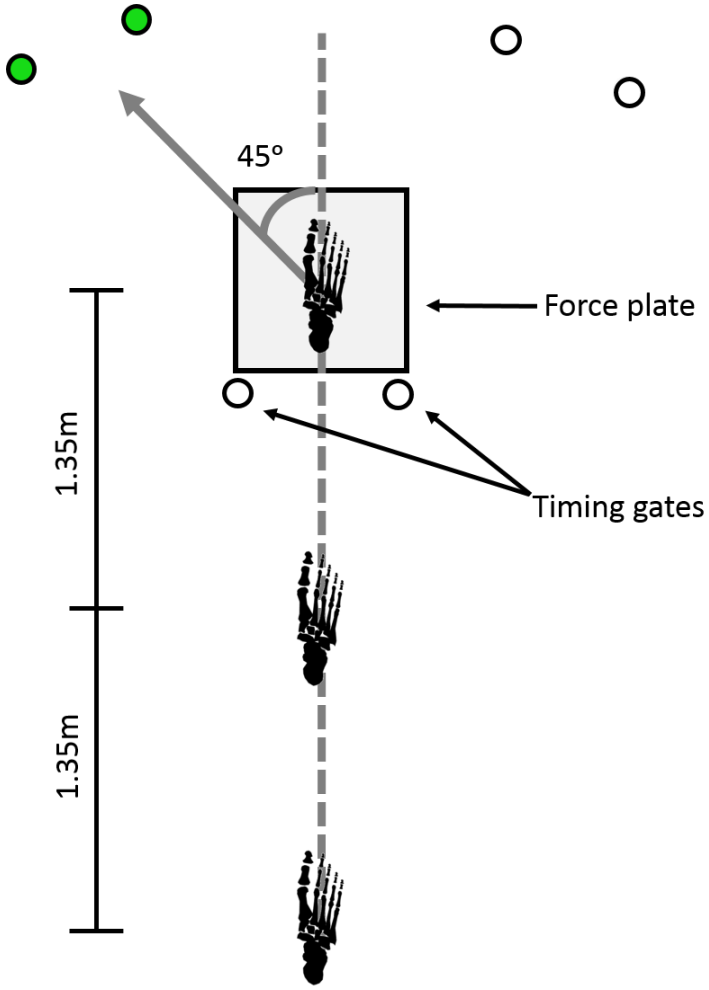

Figure 3-2. Overview of unanticipated sidestep cutting protocol from superior view. The foot indicates the required foot placement locations. Note that floor markings were used to indicate the required foot placement targets, as well as the target cutting angle of 45°. The cutting direction was randomly dictated by the timing gates, with the stimulus provided ~450ms prior to foot contact on the force plate.

3.2.4 Data processing

Marker trajectories were low-pass filtered using a zero-lag, 4th order Butterworth filter with a cut-off frequency of 8Hz. This cut-off frequency was determined via a residual analysis. GRFs were filtered using the same filter and cut-off frequency as the marker data based on published recommendations (154). EMG data were corrected for offset, high-pass filtered (20Hz), full-wave rectified and low-pass filtered (6Hz) using a zero-lag, 4th order Butterworth filter to obtain a linear envelope. EMG data were normalised to the peak amplitude obtained in each trial.

3.2.5 Musculoskeletal modelling

Musculoskeletal modelling was performed in OpenSim v3.3 (77). A generic overview of the modelling pipeline is depicted in Figure 3-3. Note that the final step (GRF decomposition) was

performed in OpenSim v3.2 due to compatibility issues with the analysis plug-in (149, 155, 156).

3.2.5.1 Musculoskeletal model

A 37 degree of freedom (DOF) full-body musculoskeletal model, with 80 musculotendon actuators (lower body) and 17 torque actuators (upper body) (76), was used to perform the musculoskeletal simulations in OpenSim (77). Each hip was modelled as a 3-DOF ball and socket joint. A pin joint was used to represent the ankle (talocrural) joint. The head-trunk segment was modelled as a single rigid segment, articulating with the pelvis via a 3-DOF ball and socket joint. Each upper limb was characterised by a 3-DOF ball and socket shoulder joint and single-DOF elbow and radioulnar joints. The subtalar, metatarsophalangeal, and wrist joints were locked (76). The knee joint was modelled differently for Chapters 5 and 7 compared to Chapter 6.

For Chapters 5 and 7, each knee was modelled as a 1-DOF hinge joint, with other rotational (valgus/varus and internal/external rotation) and translational (anteroposterior and superior-inferior) movements constrained to change as a function of the knee flexion angle (157). This method was chosen since tibiofemoral translations and non-sagittal tibiofemoral rotations are particularly susceptible to error from soft tissue artefact from skin-surface markers, especially during sidestep cutting (153).

For Chapter 6, the standard knee joint mechanism was modified to enable the computation of medial and lateral tibiofemoral contact forces via a moment-balancing approach (158).This was done by creating two hinge joints, each with an axis parallel to the anteroposterior axis of the local tibial reference frame (Figure 3-4). The superior-inferior and anteroposterior location of these contact points were placed at the knee joint centre, whilst the mediolateral location of each point was placed at a generic location in the unscaled model (159), and scaled based on each participant's femoral epicondyle width (160).

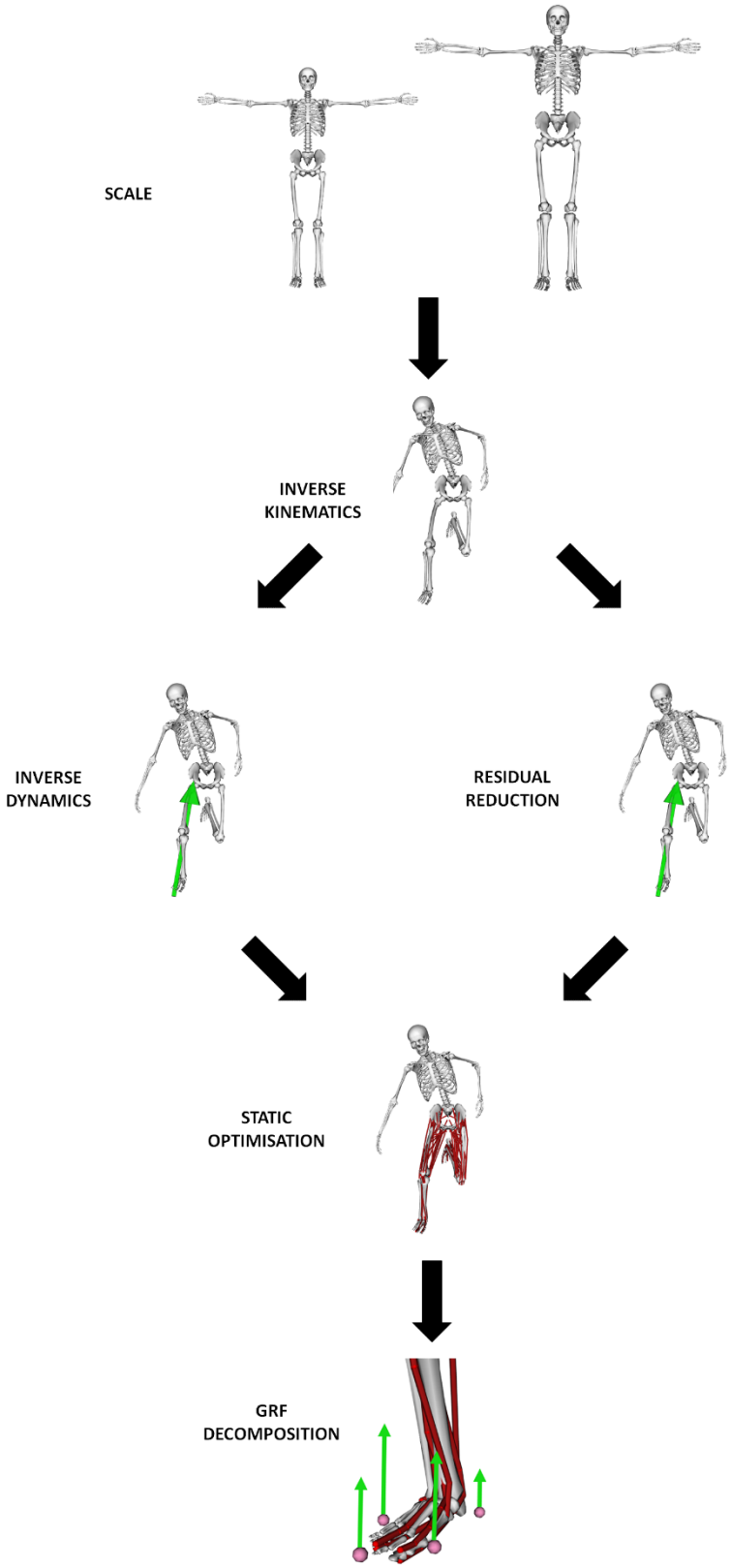

Figure 3-3. Overview of generic musculoskeletal modelling pipeline to generate simulations of unanticipated sidestep cutting. Note that the inverse dynamics step was used for Chapter 5, whilst residual reduction was used for Chapters 6 and 7. GRF, ground reaction force.

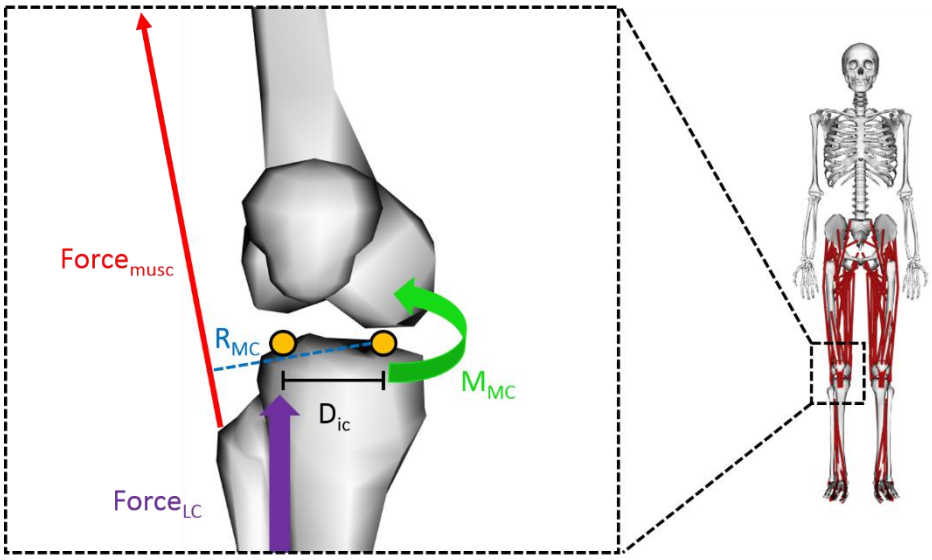

Figure 3-4. Modified knee joint mechanism to calculate medial and lateral compartment tibiofemoral contact forces. The orange circles represent the contact points. The lateral compartment contact force contribution of each muscle can be calculated as described previously by Winby et al. (158): $Force_{LC} = (Force_{musc} \times R_{MC} - M_{MC})/ D_{ic;}$ where $Force_{LC}$ is the lateral compartment contact force, $Force_{musc}$ is the muscle force of interest, R_{MC} is the moment arm of the muscle of interest about the medial contact point, M_{MC} is the external adduction moment about the medial contact point computed via inverse dynamics and D_{ic} is the distance between the contact points. Note that the medial compartment contact force contribution of each muscle can be calculated by computing the muscle force moment and the external moment about the lateral contact point. Unlike the computations by Winby et al. (158), the external adduction moment is computed by using each muscle's contribution to the ground reaction force. This method allows for consideration of dynamic coupling, and can therefore account for the influence of non-knee-spanning muscles.

3.2.5.2 Scaling

The generic model used in these simulations (76, 130) was developed based largely on average data from multiple cadavers. Updating these generic parameters for each individual required a scaling process, as many of these parameters are impossible to measure in-vivo through non-invasive means. Subsequently, the generic model was scaled to each participant's individual anthropometry in OpenSim (77). The scaling procedure in OpenSim determines a scale factor for each segment based on the relative distances between marker pairs assessed experimentally (as determined via motion capture data during the static trial) and the corresponding virtual marker pairs attached to the model. This process updates the dimensions, mass and inertial properties of each rigid segment in the generic unscaled model, as well as joint frame locations, force application points and muscle attachment points. Additionally, certain length-dependant muscle parameters, such as the optimal fibre length and tendon slack length, are also altered based on the length before and after the scaling procedure. After the scaling procedure was

completed, marker registration was used to map model markers to the same location as the experimental markers.

3.2.5.3 Inverse kinematics

An inverse kinematics algorithm was used to calculate joint angles by means of a least-squares optimisation that minimised the difference between model and experimental marker positions at each time frame (161). The global optimisation algorithm implemented in OpenSim has been shown to be capable of reducing the error introduced by soft tissue artefact from skin-surface markers (161).

3.2.5.4 Inverse dynamics

Inverse dynamics was used to obtain the generalised forces and moments at each joint that are responsible for a given movement. Specifically, inverse dynamics solves the classical equations of motion to determine the net joint forces and moments required to produce the input motion (as determined via inverse kinematics). However, these computations require the double-differentiation of joint angle positions in order to determine joint accelerations, which can result in noisy data. Additional GRF data improve the accuracy of the solution, as GRFs are sampled at a much higher rate and are less susceptible to error than joint angles. However, the inclusion of GRF data creates an over-determined system, whereby residual forces and moments can arise due to dynamic inconsistency between the kinematic and kinetic data. In reality, these forces and moments do not exist. In the present thesis, these residual forces and moments are applied to the 6-DOF joint between the pelvis and the global environment via force and torque actuators, thus enforcing dynamic consistency. These residual loads can be problematic for forward dynamic simulations (162), however inverse approaches to estimate muscle forces (such as static optimisation, described in section 3.2.5.6) can be used instead. Although having fictitious residual forces and moments is a general limitation (even with inverse approaches), it is widely accepted in the biomechanics community, especially when static optimisation is used to predict muscle forces and estimate muscle function (50, 52, 163).

3.2.5.5 Residual reduction

An alternative modelling approach is to use the residual reduction algorithm (RRA) instead of inverse dynamics, prior to muscle force predictions. This algorithm makes small adjustments to kinematics and torso inertial properties to improve dynamic consistency between kinematic data, inertial data and measured GRFs, thus reducing the requirement for residual forces and

moments applied at the pelvis. Perturbations to torso inertial properties are justified since the torso is modelled as a single rigid body, whilst in reality, it consists of numerous joints and segments. Perturbations to kinematic data are also justified since these are relatively susceptible to measurement error associated with soft tissue artefact and a lower sampling rate (compared to GRFs). Reducing residuals is particularly important for forward dynamic simulations, thus RRA is typically used prior to using the computed muscle control algorithm (115) within the OpenSim workflow. As described below, the work in this thesis used an inverse approach to estimate muscle forces, thus the use of RRA was initially not justified. However, upon further analysis, it was found that the superposition error between experimental and model predicted GRFs were large for two participants during the toe-off period. Whilst the exact reasons for this are unclear, this may be because the subtalar joint was locked during the simulations. Locking the subtalar joint is common practice and has been done by prior studies (e.g. (148, 164, 165)) to avoid issues associated with under-actuation of this joint. However, it is possible that the locked subtalar joint may have restricted natural foot kinematic characteristics for some participants, thus introducing inconsistency between kinematic data and GRFs and introducing errors into the GRF decomposition calculations. The RRA algorithm was therefore used to fix these inconsistencies for Chapters 6 and 7 (in which analysis included the toe-off period), with special care taken to ensure that foot contact patterns were not excessively altered. Note that the RRA algorithm was applied to all participants' data in Chapters 6 and 7 for consistency, and kinematic tracking errors were assessed to ensure deviations were not excessive (as defined by best practice recommendations (113)). Due to large number of user selected tracking weights for each degree of freedom, these tracking weights were optimised using a particle swarm optimisation, to minimise joint angle tracking errors whilst also lowering the residual forces and moments at the pelvis (166, 167).

3.2.5.6 Static optimisation

Various algorithms can be used to estimate muscle forces from experimentally collected motion and force data, each with inherent strengths and limitations (168). A variety of aspects need to be considered when determining which method to use, including computational efficiency, validity, and reliability. Additionally, these considerations also interact with other aspects of the study design, including the motion task being investigated, and the overall research question. Based on all of these factors, static optimisation was chosen to estimate muscle forces. Static optimisation decomposes the net joint moments into individual muscle

forces by minimising the sum of muscle activations squared, taking into account the physiological force-length-velocity properties (169) of the musculotendinous units.

This method of muscle force estimation is computationally efficient and has been used to predict muscle forces in similar high-impact movements to that investigated in the present thesis (101, 149, 170). Although muscle forces cannot be directly validated because in-vivo muscle forces are not practically feasible to measure (118), comparisons of predicted joint contact forces with in-vivo joint contact forces obtained from participants with instrumented knee implants serves as an indirect validation due to the high dependency of joint contact forces on muscle forces (118). Static optimisation has been shown to perform well in this regard, at least for walking (159, 171). Unfortunately, in-vivo joint contact force data is not available for high-impact movements such as cutting due to ethical issues. However, the suitability of static optimisation for sidestep cutting can also be assessed via qualitative comparison of the time-varying trends of the predicted muscle forces (or activations) with experimentally collected EMG data (113). This is therefore an important validation step for the work in this thesis, and is described in detail in section 3.2.5.9. As an inverse approach, the reliability of static optimisation is dependent on the reliability of the experimental input data (mass/inertial data, kinematics and GRFs). The reliability of the scaling process, as demonstrated by the Intraclass Correlation Coefficient (ICC), has been shown to be excellent for between-session reliability ($ICC \geq 0.94$), and computed segment lengths are generally within 1-2cm of magnetic resonance imaging measured segment lengths (172). These small differences in segment lengths may introduce mass/inertial errors into computations, but muscle forces estimated via static optimisation are relatively robust to these uncertainties, especially when compared to alternative muscle force estimation techniques like computed muscle control (173).Whilst reliability data for sidestep cutting is limited, Mok et al. (174) showed that, on average, kinematic and kinetic variables have excellent within-session reliability (ICC = 0.94-0.95) and good between-session reliability (ICC = 0.75-0.78). Finally, the goal of the present thesis was to describe the qualitative functional role of each muscle in contributing to tibiofemoral shear, valgus and rotation reaction loads (Chapter 5), tibiofemoral compressive forces (Chapter 6) and support, mediolateral redirection, progression and braking (Chapter 7). Subsequently, the added complexity of other muscle force estimation techniques (114-116, 175, 176) was not justified for the present work. However, subsequent to the results of the present thesis, it is acknowledged that further work may aim to use alternative, more detailed muscle force estimation techniques. For example, EMG-hybrid modelling (176), which can account for

individual muscle activation and co-contraction strategies, may be needed to guide interventions aiming to alter muscle function.

3.2.5.7 Ground reaction force decomposition

The measured GRFs were decomposed into individual muscular contributions by means of a pseudo-inverse-based approach (149, 155, 156). The work in the present thesis was based on a five-point foot-ground contact model, which incorporates time-varying kinematic constraints depending on the position of the measured centre of pressure relative to the five modelled contact points (156). Other foot-ground contact models have been used in investigations of walking and running (155, 177). However, the time-varying constraints employed by the chosen model likely provides a more realistic representation of the interaction between the foot and the ground than other single-point and/or unweighted models (155, 178), whilst remaining relatively computationally efficient (156).

3.2.5.8 Outcome variables

Outcome variables of interest were different for Chapters 5, 6 and 7. For Chapter 5, each muscle's contribution to the joint reaction forces and moments about the knee were computed by applying each muscle's force and contribution to the GRF in isolation and resolving the dynamical equations of motion. The key tibiofemoral reaction forces and moments of interest were anteroposterior shear joint reaction force as well as the frontal and transverse plane joint reaction moments. These knee joint reaction forces and moments represent the forces and moments that the knee joint experiences as a consequence of all motions and forces in the model, including muscles and other actuators. Since ACL injuries occur promptly after initial contact (10), the analysis for this chapter was limited to the weight acceptance phase (period of stance from foot-strike to the first trough in the raw vertical GRF) as per previous research (69, 146).

For chapter 6, each muscle's contribution to the medial tibiofemoral contact force was computed by using an adapted version of a previously described method (158). First, each muscle's contribution to the external adduction moment about the lateral contact point in the modified knee joint (Figure 3-4) was computed by performing inverse dynamics using the RRA-derived joint kinematics and each muscle's contribution to the GRF. Next, the muscle force-derived adduction moment about the lateral contact point was determined by multiplying each muscle force of interest by its respective moment arm about the lateral contact point. In the case of non-knee-spanning muscles, this term was zero due to no moment arm about either contact point in the knee. The difference between the muscle force-derived adduction moment

and muscle derived external adduction moment was then divided by the distance between the contact points. This same procedure was used to calculate muscle force contributions to the lateral contact force by performing calculations about the medial contact point.

For chapter 7, muscular contributions to "support" as well as "braking and propulsion" were defined by their contributions to the vertical and anteroposterior GRFs, respectively. Muscular contributions to the mediolateral GRF have been investigated during walking, and are typically described as "balance" (51, 52). However, change-of-direction manoeuvres require appreciable acceleration of the body's centre-of-mass out of the sagittal plane, thus muscular contributions to the mediolateral GRF were considered as "redirection". Finally, consistent with other studies investigating muscle function (e.g. (52, 149)), muscular contributions to lower-limb joint moments were also computed.

Muscular contributions for Chapters 5, 6, and 7 were grouped according to function consistent with a prior approach (107), except where these muscles had opposing effects on the key parameters. For example, the biceps femoris long head and medial hamstrings (i.e. semimembranosus and semitendinosus) have opposing transverse plane actions at the knee, hence the biarticular hamstrings were not grouped together for Chapters 5 and 6. For Chapter 7, the biarticular hamstrings were grouped together, since their contributions to the vertical and anteroposterior GRF were similar, whilst their contribution to the mediolateral GRF were minimal. Note that only major muscle groups are reported on, and the reader is referred to Rajagopal et al. (76) for all musculotendinous actuators included in the model.

3.2.5.9 Validation and verification

Validation and verification of model predictions were performed in accordance with current best practice guidelines (113). Qualitative comparisons between the model-based predicted activations and experimental EMG data were performed whilst accounting for appropriate physiological delays (~100ms) as per current recommendations (113). EMG data were obtained from experimental recordings from the present work and from available data in the literature (46, 147). Since these comparisons were conducted to assess how well the simulations replicated the coordination pattern observed experimentally, the normalised EMG data were averaged across participants and then renormalised to the peak amplitude of each muscle. The predicted activations were processed using the same normalisation procedure as the EMG data, prior to these comparisons. These qualitative comparisons were conducted across the entire stance phase, even for Chapter 5, because the weight acceptance phase was generally too short

to allow any firm conclusions to be made about how well the model-based predicted data temporally matched experimental data as well as data obtained from the literature.

The time-varying characteristics of the experimental joint angles and inverse dynamics based joint moments were compared to ensure they were within 2SD of prior published data for Chapter 5 (113). For Chapters 6 and 7, a similar comparison to published data were performed for the RRA-derived joint angles and moments.

Quantitative verification that the muscle-derived joint moments (computed from the predicted muscle forces and their respective moments arm) matched the experimentally measured joint moments (computed via inverse dynamics in Chapter 5, and RRA in Chapters 6 and 7) was performed by calculating the normalised root mean square error (nRMSE) and coefficient of determination (R^2). The nRMSE was calculated as:

$$\text{nRMSE}\ (\%) = 100 \times \frac{\sqrt{\frac{\sum_{i=1}^{n} (Experimental_i - Predicted_i)^2}{n}}}{\max(Experimental) - \min(Experimental)}$$

To verify the suitability of the foot-ground contact model, superposition errors between experimental and simulated GRFs were quantitatively evaluated via computation of the nRMSE and R^2. These data were reported as the median and interquartile range (IQR) due to non-normal distributions.

For Chapters 6 and 7, the root mean square and maximum kinematic tracking errors between joint angles derived from inverse kinematics and those derived from RRA were assessed to ensure they were reasonable (113).

Chapter 4 – Study 1: Systematic Review and Meta-analysis

Publication statement:

This chapter is comprised of the following paper published in *The British Journal of Sports Medicine*:

Maniar, N, Shield, A.J, Williams, M.D., Timmins, R.G; & Opar, D.A. (2016) Hamstring strength and flexibility after hamstring strain injury: a systematic review and meta-analysis. *British Journal of Sports Medicine*, *50*(15). 909-920. doi: 10.1136/bjsports-2015-095311.

4.1 Linking paragraph

As described in Chapter 2, the hamstrings have considerable evidence as the primary agonist to the anterior cruciate ligament (ACL), as they induce reaction forces and moments at the knee which ultimately results in unloading of the ACL. This suggests that any condition where force production of the hamstrings is impaired could be associated with increased risk of ACL injury. One such condition is hamstring strain injury (HSI). Many prior studies have performed retrospective investigations of hamstring strength following HSI. These studies often have different conclusions, thus synthesis of the present literature was warranted. Subsequently, Chapter 4 was a systematic review and meta-analysis of hamstring strength following HSI. Since hamstring flexibility is also commonly monitored after HSI, this data was also synthesised due to high relevance for clinicians.

A secondary aim of this paper was to determine, across the literature, the breadth of data collected in individuals following HSI. Given the multi-planar risk profile associated with increased knee joint loading, understanding if other lower-limb muscles or multi-planar movements are examined post-HSI is important information to determine what further work needs to be done to better study an association between prior HSI and future ACL injury. As part of the peer-review process for this paper, the information pertaining to the secondary aim was removed from the manuscript at the direction of the editor and reviewers. The pertinent data for the thesis addressing the secondary aim is presented as information supplementary to the published manuscript in section 4.8.

4.2 Abstract

Hamstring strain injuries (HSIs) are the most common non-contact injury in many high intensity running based sports. Relatively high recurrence rates have prompted many retrospective investigations of hamstring function following HSI. Such data could be used to inform rehabilitation practices aiming to reduce recurrence rates. Subsequently, the aim of this investigation was to systematically review and meta-analyse the evidence base related to hamstring strength and flexibility in previously injured hamstrings. A systematic literature search was conducted of PubMed, CINAHL, SPORTDiscus, Cochrane library, Web of Science, and EMBASE from inception to August 2015. Full text English articles which included studies which assessed at least one measure of hamstring strength or flexibility in men and women with prior HSI within 24 months of the testing date. Studies were required to have an uninjured comparison group (contralateral leg or uninjured control group). Twenty eight studies were included in the review, which in total included 898 participants. Previously injured legs demonstrated deficits across several variables. Lower isometric strength was found <7 days post injury (effect size, -1.72, 95%CI, -3.43 to 0.00), but this did not persist beyond 7 days after injury. The passive straight leg raise was restricted at multiple time points after injury (<10 days, effect size, -1.12, 95%CI, -1.76 to -0.48; 10-20 days, effect size, -0.74, 95%CI, -1.38 to -0.09; 20-30 days, effect size, -0.40, 95%CI, --0.78 to -0.03), but not at 40-50 days post injury. We report deficits that remained after return to play in isokinetically measured concentric (60°/sec, effect size, -0.33, 95%CI, -0.53 to -0.13) and Nordic eccentric knee flexor strength (effect size, -0.39, 95%CI, -0.77 to 0.00). The conventional hamstring to quadriceps strength ratios were also reduced well after return to play (60:60°/sec , effect size, -0.32, 95%CI, -0.54 to -0.11; 240:240°/sec , effect size, -0.43, 95%CI, -0.83 to -0.03) and functional (30:240°/sec, effect size, -0.88, 95%CI, -1.27 to -0.48) but these effects were inconsistent across measurement velocities/method. In conclusion, isometric and passive straight leg raise deficits resolve within 20-50 days following HSI. Deficits in eccentric and concentric strength and strength ratios persist after return to play, but this effect was inconsistent across measurement velocities/methods. Flexibility and isometric strength should be monitored throughout rehabilitation, but dynamic strength should be assessed at and following return to play.

4.3 Introduction

Hamstring strain injuries (HSIs) are the most common non-contact injury in Australian rules football (179-183), soccer (184-188), rugby union (189-192), track and field (193-195) and American football (196). HSIs result in time away from competition (187), financial burden (187, 197) and impaired performance upon return to competition (198). Further to this, recurrent hamstring strain often leads to a greater severity of injury than the initial insult (188, 192). The most commonly cited risk factor for future HSI is a previous HSI (199-202). The high recurrence rates of HSI (188, 192) are proposed to result from incomplete recovery and/or inadequate rehabilitation (203, 204) because of pressure for early return to play at the expense of convalescence (205). Consequently, there has been much interest recently in observations of hamstring structure and function in previously injured legs compared to control data (35-37, 206-209). Despite the possible limitation of this approach, it is often agreed that deficits that exist in previously injured hamstrings could be a maladaptive response to injury (210). As such, these deficits that persist beyond return to play could provide markers to better monitor athletes during and/or at the completion of rehabilitation (210).

Which parameters are the best markers to monitor an athlete's progress during rehabilitation? Conventional clinical practice focuses on measures of strength and flexibility, however the evidence is based on predominantly retrospective observations of strength (35, 206, 211-217), strength ratios (211, 212, 214, 215, 218, 219), and flexibility (135, 204, 206, 217, 220-223) in previously injured athletes. These studies were limited in reporting single or isolated measures with methodologies and populations that differed from study to study. To advance knowledge, we aimed to systematically review the evidence base related to hamstring strength and flexibility in previously injured hamstrings.

4.4 Methods

4.4.1 Literature search

A systematic literature search was conducted of PubMed, CINAHL, SPORTDiscus, Cochrane library, Web of Science, and EMBASE from inception to August 2015. Key words (Table 4-1) were chosen in accordance with the aims of the research. Retrieved references were imported into Endnote X7 (Thomson Reuters, New York, USA), with duplicates subsequently deleted. To ensure all recent and relevant references were retrieved, citation tracking was performed via Google Scholar and reference list searches were also conducted.

Table 4-1. Summary of keyword grouping employed during database searches.

Muscle Group	Injury	Time
Hamstring*	Injur*	Past
Semitendinosus	Strain*	Prior
Semimembranosus	Tear	Retrospective*
"Biceps Femoris"	Rupture*	Previous*
"Posterior Thigh"	Pull*	Recent*
Thigh	Trauma	Histor*
	Torn	

*truncation. Boolean term OR was used within categories, whilst AND was used between categories.

4.4.2 Selection criteria

Selection criteria were developed prior to searching to maintain objectivity when identifying studies for inclusion. To address the aims, included papers had to:

- assess at least one parameter of hamstring strength (maximum strength, associated strength ratios and angle of peak torque) or flexibility in humans with a prior HSI within the prior 24 months of testing
- have control data for comparison, (whether it was a contralateral uninjured leg or an uninjured group) and
- have the full text journal article in English available (excluding reviews, conference abstracts, case studies/series)
- not include hamstring tendon or avulsion injuries as these are a different pathology

The titles and abstracts of each article were scanned by one author (NM) and removed if information was clearly inappropriate. Selection criteria were then independently applied to the remaining articles by three authors (NM, RT and DO). Full text was obtained for remaining articles, with selection criteria reapplied by one author (NM) and cross referenced by another author (DO).

4.4.3 Analysis

4.4.3.1 Assessing bias and methodological quality

Risk of bias assessment was performed independently by two examiners. We used a modified version of a checklist by Downs and Black (224). The original checklist contained 27 items, however many were relevant only to intervention studies. Since the majority of the papers in

this review were of a retrospective nature, items 4, 8, 9 13, 14, 15, 17, 19, 22, 23, 24, and 26 were excluded as they were not relevant to the aims of the review.

Of the remaining items, 1, 2, 3, 5, 6, 7, and 10 assessed factors regarding the reporting of aims, methods, data and results, whilst items 16, 18, 20, 21, and 25 assessed internal validity and bias. Item 27 was not suitable to the context of the current review, and was modified to address power calculations. Two new items (items 28 and 29) relating to injury diagnosis and rehabilitation/interventions were added to more appropriately assess the risk of bias and thus the modified checklist contained 17 items (Appendix II Table 2).

Fourteen of the items were scored 0 if the criterion was not met or it was unable to be determined, whilst successfully met criteria were scored 1 point. The other three items (items 5, 28 and 29) were scored 0, 1 or 2 points, as dictated by the criteria presented in Appendix II Table 2. This resulted in a total of 20 points available for each article.

Similarly modified versions of this checklist has been used in previous systematic reviews investigating factors leading to heel pain (225) and risk factors associated with hamstring injury (226). The risk of bias assessment was conducted by two authors (NM and DO), with results expressed as a percentage. In the case of disagreement between assessors, an independent individual was consulted with consensus reached via discussion if necessary. In situations where one of the assessors (DO) was a listed author on a study included for review, the independent individual completed the risk of bias assessment in their place.

4.4.3.2 Data Extraction

Relevant data was extracted including the participant numbers, population and sampling details, diagnosis technique, severity of injury, time from injury to testing (in days assuming 30.4 days per month, 365 days per year), variables investigated and how these were tested, results including statistical analysis, and, where appropriate, potential confounders that may affect strength or flexibility outcomes. The major confounders include other lower-limb injuries likely to affect strength and flexibility, interventions and rehabilitation programs performed. Furthermore, insufficient evidence exist regarding the interaction between gender and HSI, thus mixed gender cohorts were considered as a potential confounder.

4.4.3.3 Data Analysis

Although objectively synthesizing evidence via a meta-analysis is often desirable, this technique was not able to be applied to the all the evidence retrieved in this review, due to insufficient reporting of data (i.e. two or more studies or subgroups with mean, standard

deviation, and participant numbers for contralateral leg comparisons) or methodological variations between studies.

When sufficient data was available, meta-analysis and graphical outputs were performed using selected packages (227-229) on R (230). Standardised mean differences (Cohen's *d*) facilitated the comparison of studies reporting variables in different units, with effect estimates and 95% confidence intervals summarised in forest plots. A random effects model was used to determine the overall effect estimate of all studies within the variable or subgroup as appropriate, with variance estimated through a restricted maximum likelihood (REML) method. The magnitudes of the effect size were interpreted as small (d = 0.20), moderate (d = 0.50) and large (d = 0.80) according to thresholds proposed by Cohen (231). Where studies reported multiple types of data (e.g. multiple isokinetic velocities, multiple subgroups or multiple time points), these data were analysed as subgroups to avoid biasing the weighting of the data. These time bands were dictated by the data available. Where data were available in the acute stages (prior to return to play), time bands were kept at less than 10 days as it would be expected that deficits would change relatively rapidly during this time, due to on-going rehabilitation and recovery.

Data presented for participants at or after return to play were pooled for two reasons, 1) no included study reported any on-going rehabilitation after return to play and 2) many of these studies had variable time from injury until testing between individual participants. Where a study had multiple time-points that fit within post return to play time-band (e.g. at return to play and follow-up), the earlier option was chosen as there was expected to be a lower chance of bias due to other uncontrolled or unmonitored activities. For the purposes of meta-regression (employed to assess the effects of time since injury), studies with multiple time points were pooled to provide the best assessment of the effect of time on the given variable. Therefore, each subgroup/time point was considered as a unique study, allowing sufficient data (>10 subgroups) for meta-regression analysis (232) providing that time from injury until testing was reported. Funnel plots were visually inspected for asymmetry to assess publication bias. Heterogeneity was determined by the I^2 statistic, and can be interpreted via the following thresholds (232):

- 0-40%: might not be important
- 30-60%: may represent moderate heterogeneity
- 50-90%: may represent substantial heterogeneity
- 75-100%: considerable heterogeneity

In situations where it was deemed that reported data (i.e. mean, standard deviation, participant numbers for contralateral leg comparisons) was insufficient for meta-analysis and could not be obtained via supplementary material or from contacting the corresponding author, a best evidence synthesis (233) was employed. The level of evidence was ranked according to criteria consistent with previously published systematic reviews (234, 235) as outlined below:

- Strong: two or more studies of a high quality and generally consistent findings (≥75% of studies showing consistent results)
- Moderate: one high quality study and/or two or more low quality studies and generally consistent findings (≥75% of studies showing consistent results),
- Limited: one low quality study,
- Conflicting: inconsistent findings (<75% of studies showing consistent results),
- None: no supportive findings in the literature

A high quality study was defined as a risk of bias assessment score of ≥70% whereas a low quality study had a risk of bias assessment score <70% (232).

4.5 Results

4.5.1 Search results

The search strategy consisted of six steps (Figure 4-1). The initial search yielded 7805 items (Cochrane library = 131; PubMed = 2407, CINAHL = 604; SPORTDiscus = 640; Web of Science = 1049; EMBASE = 2974) from all databases. After duplicates were removed, 4306 items remained. Title and abstract screening resulted in 92 remaining articles, reference list hand searching and citation tracking resulted in the addition of 7 articles. Independent application of the selection criteria yielded 28 articles to be included in the review, 23 of which were included in meta-analysis.

4.5.2 Risk of bias assessment

Risk of bias assessment of each article is displayed in Table 4-2. It is important to note that the risk of bias assessment was not the basis of exclusion. Included articles ranged from a score of 8 to 18 of a possible 20(40% – 90%).

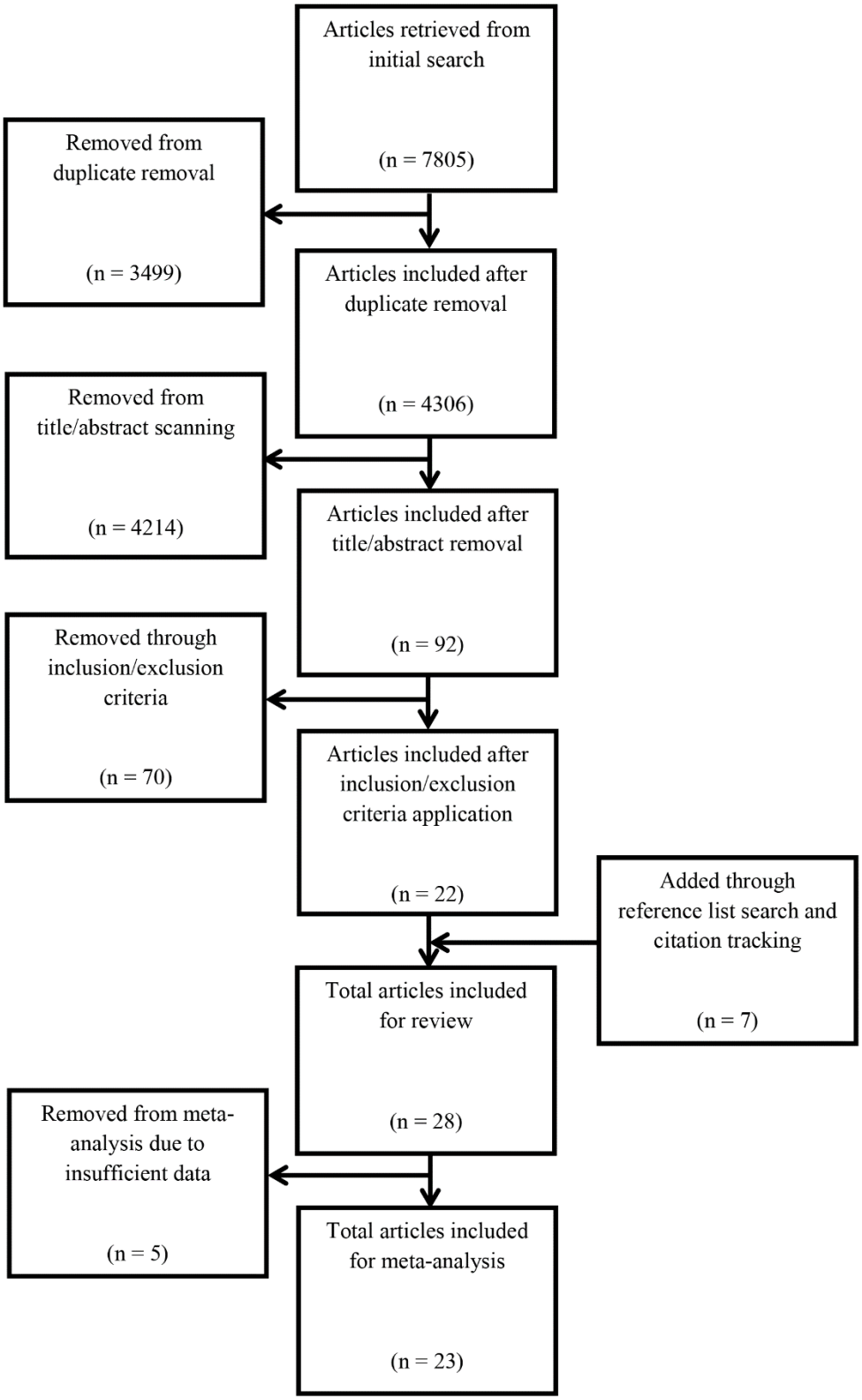

Figure 4-1. Flow diagram outlining steps for study inclusion/exclusion.

4.5.3 Description of studies

4.5.3.1 Participants

A sample of 898 participants (*n* = 802 male, *n* = 96 female; age range, 15-47 years) were examined across the included studies. Seventeen studies included only male participants (35, 37, 135, 143, 211, 212, 214-218, 220, 221, 223, 236-238), ten studies had mixed gender (204, 206, 209, 222, 239-244), whilst only one exclusively studied females (245). Participants were generally considered recreationally active at a minimum.

4.5.3.2 Injury

Methods of diagnosis varied between studies, with some studies using multiple methods of diagnosis. Twelve studies used clinical criteria (37, 135, 204, 206, 209, 211, 212, 217, 239, 241-243), ten used magnetic resonance imaging (MRI) (35, 37, 204, 206, 209, 237, 239, 240, 242, 243), five had medical or health practitioner diagnosis (135, 214, 216, 218), seven used a questionnaire or self-report (215, 221-223, 236, 238, 245), two used ultrasound (211, 212), and two had unclear methods of diagnosis (220, 244). Description of severity of injury varied significantly between studies, with the most common being time to return to play (35, 135, 204, 206, 215, 217, 218, 223, 238, 239) and grade (I-III) of injury (35, 209, 214, 237, 241-244). Description of time from injury to testing varied significantly between studies (range, 2-690 days).

4.5.3.3 Outcomes

The strength variables examined were concentric, eccentric and isometric (absolute and normalised to body mass), strength ratios (usually hamstring to quadriceps (H:Q)), and angle of peak torque. The five flexibility variables examined were passive straight leg raise, active straight leg raise, passive knee extension, active knee extension and the sit and reach. All five strength variables (concentric, eccentric, isometric, strength ratios, angle of peak torque) and three flexibility variables (passive straight leg raise, active knee extension, and passive knee extension) were included for meta-analysis. Sufficient data were available to run meta-regression analysis for isometric strength, the passive straight leg raise and the passive knee extension. The best evidence synthesis method was applied to remaining variables for which insufficient data were available for meta-analysis. The best evidence synthesis is summarised in Table 4-3.

Table 4-2. Itemised scoring of study quality using a modified (Appendix II Table 2) Downs and Black checklist (224).

First author, year	1	2	3	5	6	7	10	11	12	16	18	20	21	25	27	28	29	Total	%	Quality
Arumugam 2015	0	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	0	10	50	Low
Askling 2006	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	2	1	14	70	High
Askling 2010	1	1	1	1	1	1	0	0	0	1	1	1	1	0	0	2	0	12	60	Low
Brockett 2004	1	1	1	1	1	0	1	0	0	1	1	1	1	0	0	1	1	12	60	Low
Croisier 2000	1	1	1	1	1	1	0	0	0	1	1	1	0	1	0	1	0	11	55	Low
Croisier 2002	1	1	1	1	1	1	0	0	0	1	0	1	1	1	0	2	0	12	60	Low
Dauty 2003	1	1	0	1	1	1	0	0	0	1	1	1	1	1	0	1	0	11	55	Low
Doherty 2012	1	1	1	1	0	1	1	0	0	1	1	1	1	1	0	0	0	11	55	Low
Hennessy 1993	1	1	0	0	1	1	0	0	0	1	1	1	1	0	0	0	0	8	40	Low
Jonhagen 1994	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	12	60	Low
Lee 2009	1	1	1	1	1	1	1	0	0	1	1	0	1	1	0	1	0	12	60	Low
Lowther 2012	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	0	11	55	Low
Mackay 2010	1	1	1	1	1	1	1	0	0	1	1	1	1	0	0	0	0	11	55	Low
Opar 2013a	1	1	0	1	1	1	1	0	0	1	1	1	1	1	0	2	0	13	65	Low
Opar 2013b	1	1	1	2	1	1	1	0	0	1	1	1	1	1	0	1	1	15	75	High
Opar 2015	1	1	1	2	1	1	1	0	0	1	1	1	1	1	1	2	0	16	80	High
O'Sullivan & Burns 2009	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	12	60	Low
O'Sullivan 2009	1	1	1	1	1	1	1	0	0	1	1	1	1	1	0	0	0	12	60	Low
O'Sullivan 2008	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	0	11	55	Low
Reurink 2015	1	1	1	2	1	1	1	0	0	1	1	1	1	1	1	2	2	18	90	High
Reurink 2013	1	1	1	2	1	1	1	0	0	1	1	1	1	1	1	2	2	18	90	High
Sanfilippo 2013	1	1	1	2	1	1	1	0	0	1	1	1	1	1	0	2	2	17	85	High
Silder 2010	1	1	1	1	1	1	1	0	0	1	1	1	0	1	0	2	1	14	70	High
Silder 2013	1	1	1	2	1	1	1	0	0	1	1	1	1	1	0	2	2	17	85	High
Sole 2011	1	1	1	1	1	1	1	0	0	1	1	1	0	1	0	1	0	12	60	Low
Timmins 2015	1	1	1	1	1	1	1	0	0	1	1	1	1	1	1	2	1	16	80	High
Tol 2014	1	1	0	1	1	1	1	0	0	1	1	1	1	1	0	2	2	15	75	High
Worrell 1991	1	1	1	1	1	1	0	0	0	1	1	1	1	1	0	0	0	11	55	Low

A high quality study was defined as a risk of bias assessment score of ≥70% whereas a low quality study had a risk of bias assessment score <70

4.5.4 Strength

4.5.4.1 Concentric Strength

Data for all studies which examined concentric strength can be found in Appendix II Table 3.

Meta-analysis. Concentric strength was measured isokinetically at 60 (35, 135, 215, 236-239, 241, 245), 180 (35, 215, 236, 245) and 300°/sec (214, 215, 237, 245). A statistically significant small effect for lower concentric strength at 60°/sec was found in previously injured legs (effect size, -0.33; 95%CI, -0.53 to -0.13; I^2, 0%), but no significant effects were found at 180 or 300°/sec (Figure 4-2).

Best evidence synthesis. Of the dynamic strength variables which were not included in the meta-analysis, one (seated isokinetic at 240°/sec) (211, 212, 239) had moderate evidence for a decrease in strength in the previously injured hamstrings. Concentric strength at 270°/sec in a seated position (217) had limited evidence and concentric strength at 60°/sec in a prone position (223) had no supporting evidence.

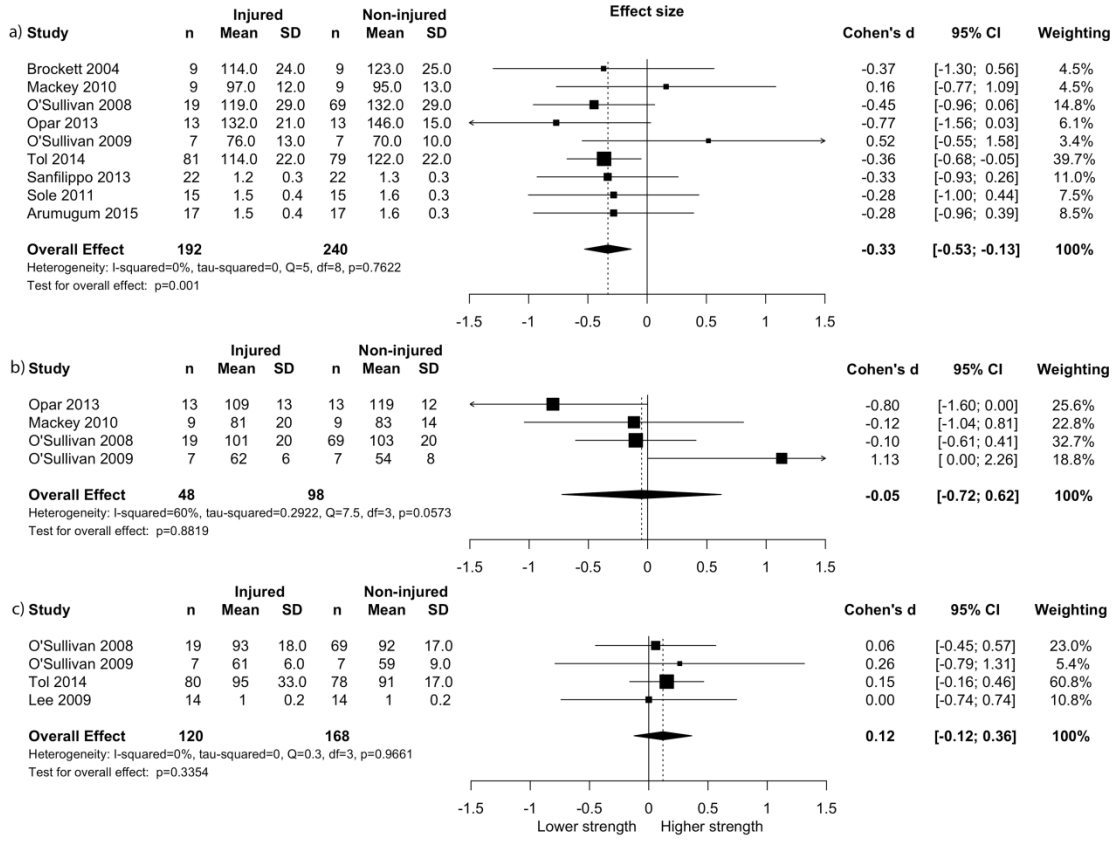

Figure 4-2. Forest plot of concentric strength measured at a) 60°/sec, b) 180°/sec, and c) 300°/sec.

4.5.4.2 Eccentric strength

Data for all studies which examined eccentric strength can be found in Appendix II Table 4.

Meta-analysis. Eccentric strength measured during the Nordic hamstring exercise (37, 143, 216) and isokinetically at 60 (35, 135, 237, 238, 244) and 180°/sec (35, 244) were included in the meta-analysis. Significant deficits in previously injured legs were found for eccentric strength measured via the Nordic hamstring exercise (effect size, -0.39; 95%CI, -0.77 to 0.00; I^2, 0%), but no other method (Figure 4-3).

Best evidence synthesis. Eccentric isokinetic strength measured at 30 (211, 212, 217, 236) and 120°/sec (211, 212) had moderate evidence, indicating lower strength in previously injured hamstrings, whereas measures at 230 (217) and 300°/sec (214) had limited evidence. The measurement of eccentric strength at 60°/sec in a prone position (223) had no supporting evidence.

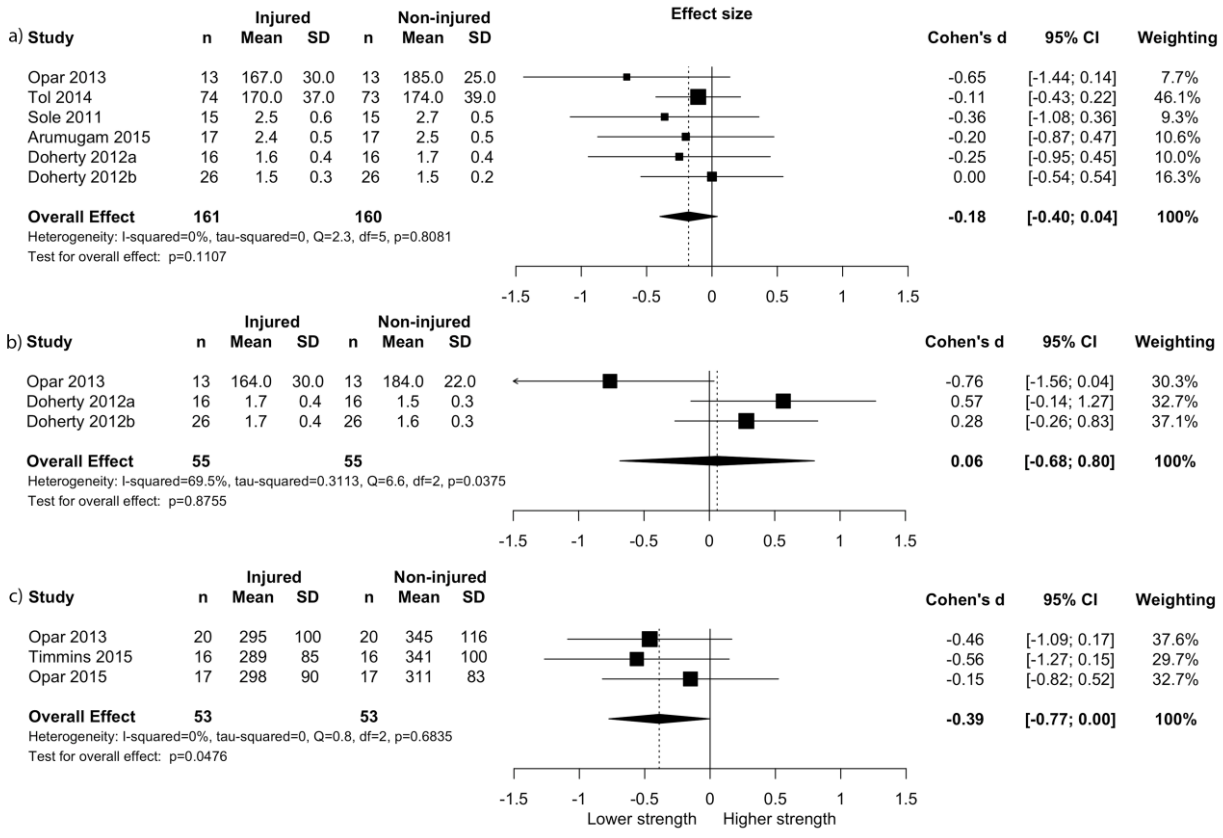

Figure 4-3. Forest plot of eccentric strength measured at a) 60°/sec, b) 180°/sec, and c) during the Nordic hamstring exercise. Note that one study (244) had two subgroups, a, Division III athletes; b, Division I athletes.

Table 4-3. Best evidence synthesis data for all major categories of outcome variables assessed in individuals with a prior hamstring strain injury.

Variable	Testing method	No. of studies	Consistency (%)			Quality (mean ± SD)	Level of evidence of difference
			Decrease	No change	Increase		
Concentric strength*	Seated isokinetic (240°/sec)	3	100	0	0	67 ± 16	Moderate
Eccentric strength	Seated isokinetic (30°/sec)	4	75	25	0	58 ± 3	Moderate
Eccentric strength	Seated isokinetic (120°/sec)	2	100	0	0	58 ± 4	Moderate
Isometric Strength[#]	Hip, 0°; knee, 90°	1	100	0	0	90	Moderate
Concentric strength	Seated isokinetic (270°/sec)	1	100	0	0	60	Limited
Eccentric strength	Seated isokinetic (230°/sec)	1	100	0	0	60	Limited
Eccentric strength	Seated isokinetic (300°/sec)	1	100	0	0	60	Limited
Eccentric Hamstring:Hip flexor peak torque ratio	Seated/standing isokinetic (300°/sec)	1	100	0	0	60	Limited
Eccentric angle of peak torque	Seated isokinetic (30°/sec)	1	0	0	100	55	Limited
Flexibility[¥]	Passive knee extension	3	67	33	0	57 ± 3	Conflicting
Flexibility	Active straight leg raise	2	50	50	0	50 ± 14	Conflicting

Consistency refers to the percentage of studies showing a particular outcome; *, one study (239) showed deficit present at return to play and 6-months post injury; [¥], deficit assessed post return to play; [#], deficit present at initial evaluation and 7-day follow-up.

4.5.4.3 Isometric Strength

Data for all studies which examined isometric strength can be found in Appendix II Table 5.

Meta-analysis. Isometric strength measured at long muscle lengths (hip, 0°; knee, 0-15°) was included in the meta-analysis (37, 206, 242). Measures were taken at multiple time-points (<7 days, 7-14, 21, 42, and >180 days) post injury, thus subgroups were analysed (Figure 4-4) and meta-regression was performed. A large effect for lower long-length isometric strength was statistically significant in previously injured legs compared to the uninjured contralateral legs less than seven days post injury (effect size, -1.72; 95%CI, -3.43 to 0.00; I^2, 91%), but not at any other time point. Meta-regression analysis (Figure 4-5) revealed no significant effect for time since injury for isometric strength (intercept, -0.92, p = 0.002; coefficient, 0.003, p = 0.292).

Best evidence synthesis. One study (242) assessed isometric strength in a short muscle length (hip 0°, knee 90°). This study did not statistically test for differences between muscles, but based on effect size and confidence intervals, isometric strength was reduced at the initial evaluation (effect size, -0.74; 95%CI, -1.07 to -0.41), and at the 7 day follow-up (effect size, -0.39; 95%CI, -0.71 to -0.07) but not the 26 week follow-up (effect size, -0.12; 95%CI, -0.45 to 0.20).

4.5.4.4 Hamstring:Quadriceps Torque Ratio

Data for all studies which examined H:Q ratios can be found in Appendix II Tables 6 and 7.

Meta-analysis. The conventional H:Q ratio, whereby peak torque of each muscle group is assessed during concentric isokinetic contraction at 60:60 (135, 211, 212, 215, 218, 236, 244, 245), 180:180 (215, 236, 244, 245), 240:240 (211, 212), and 300:300°/sec (214, 215, 245) (Figure 4-6). A statistically significant small effect for a lower conventional H:Q ratio was found in previously injured legs compared to the uninjured contralateral legs at 60:60 (effect size, -0.32; 95%CI, -0.54 to -0.11; I^2 = 0%) and 240:240°/sec (effect size, -0.43; 95%CI, -0.83 to -0.03; I^2, 0%), but not 180:180 and 300:300°/sec. Meta-analysis of the functional H:Q (fH:Q), whereby the hamstring group is assessed eccentrically, but the quadriceps groups is assessed concentrically, included isokinetic velocities 30:240 (211, 212, 239) and 60:60°/sec (135, 218, 238, 244) (Figure 4-7). A large effect was found for a lower ratio was found in previously injured legs at 30:240°/sec (effect size, -0.88; 95%CI, -1.27 to -0.48; I^2, 0%), but no significant differences between injured and uninjured legs at 60:60°/sec.

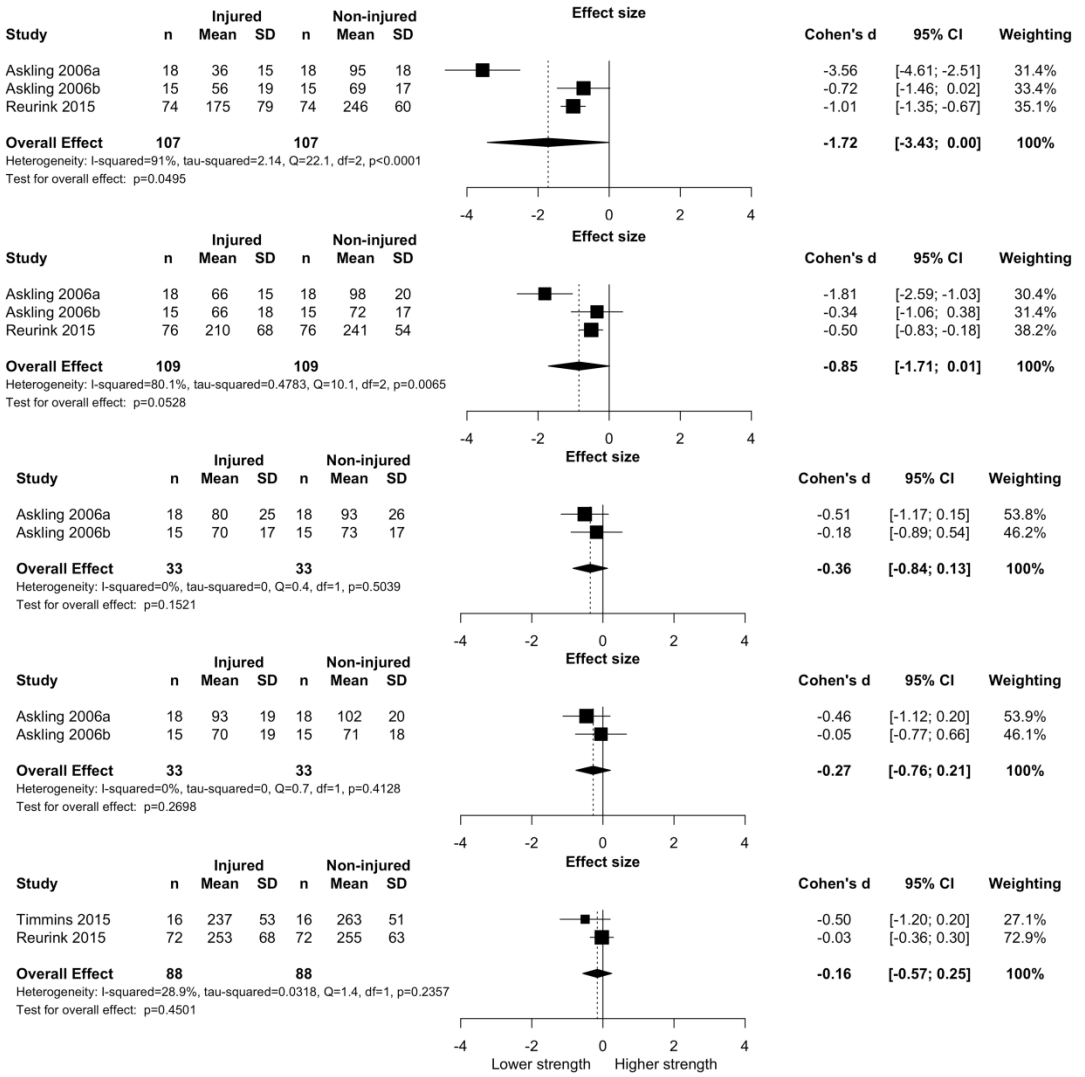

Figure 4-4. Forest plot of isometric strength assessed at a) <3 days post injury, b) 10 days post injury, c) 21 days post injury, d) 42 days post injury and e) >180 days post injury

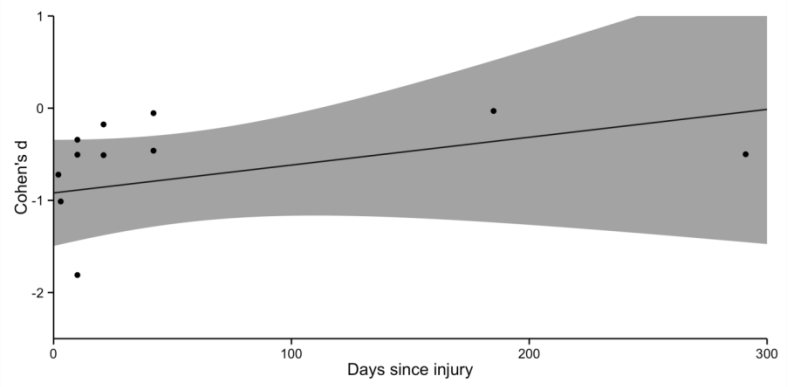

Figure 4-5. Meta-regression plot (with 95%CI) for isometric strength. Intercept, -0.92, p = 0.002; coefficient, 0.003, p = 0.292.

Best evidence synthesis. One study which examined H:Q (60:60°/sec) (223) was not included in the meta-analysis due to the prone and supine position in which knee flexor and quadriceps strength were assessed respectively. This study found no significant difference between injured and uninjured legs. No supporting evidence was found for the fH:Q strength ratio at 180:180 (244), 30:60, 30:180°/sec (236) and limited evidence found for 300:300°/sec (214). The eccentric H:Q, whereby both knee flexor and quadriceps strength are assessed via eccentric contractions was assessed isokinetically in prone/supine (223) position. Neither study found any differences between previously injured and uninjured legs. Limited evidence was found for eccentric knee flexor torque to concentric hip flexor torque ratio deficits in previously injured legs (effect size, -0.9) compared to uninjured contralateral legs (214).

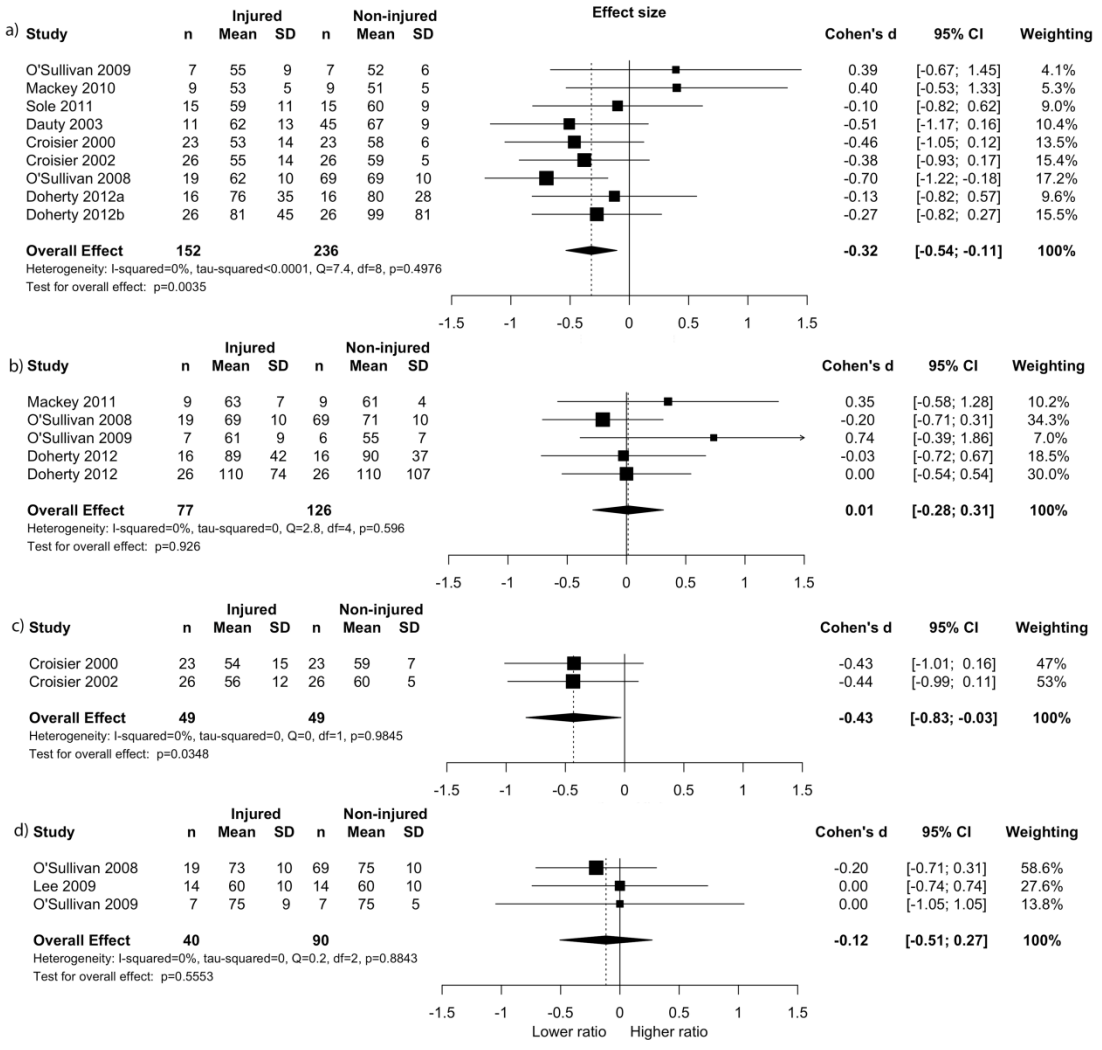

Figure 4-6. Forest plot of conventional H:Q ratio assessed at a) 60:60°/sec, b) 180:180°/sec, c) 240:240°/sec, and d) 300:300°/sec. Note that one study (244) had two subgroups, a, Division III athletes; b, Division I athletes.

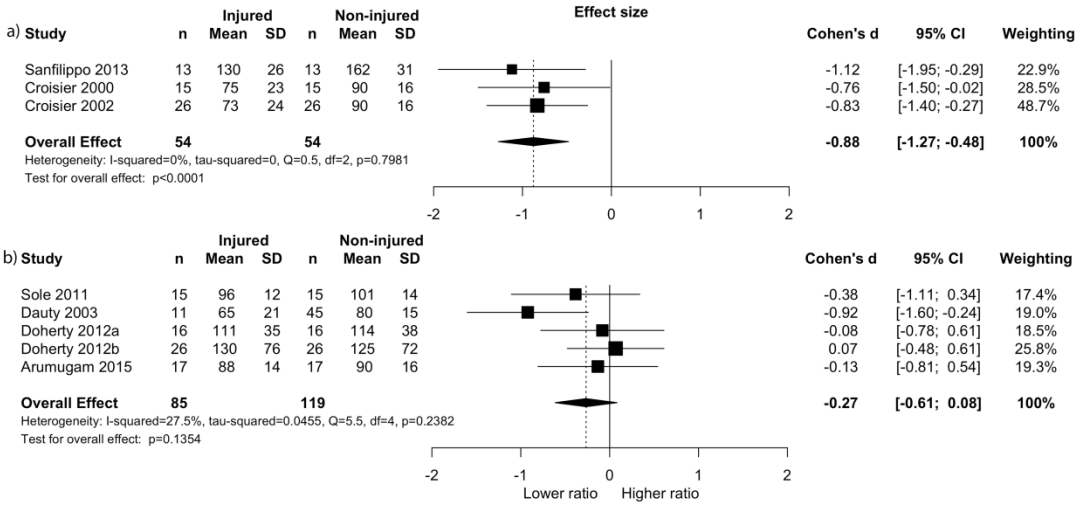

Figure 4-7. Forest plot of the fH:Q ratio assessed at a) 30:240°/sec and b) 60:60°/sec. Note that one study (244) had two subgroups, a, Division III athletes; b, Division I athletes.

4.5.4.5 Angle of peak torque

Data for all studies which examined optimal angle of peak torque can be found in Appendix II Table 8.

Meta-analysis. The optimal angle of peak torque (concentric 60°/sec) had sufficient data (236, 239, 241) for meta-analysis. No significant differences between injured or uninjured legs were found (Figure 4-8).

Best evidence synthesis. Limited evidence was found for the eccentric angle of peak torque to occur at significantly shorter muscle lengths in the injured legs compared to the uninjured contralateral legs at 30°/sec (236). No differences were found for angle of peak torque between legs/groups at 240 (239) and 300°sec (214) concentrically or 300°/sec (214) eccentrically measured angle of peak torque.

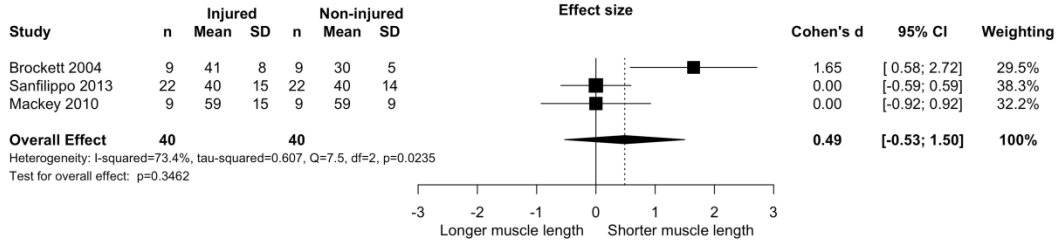

Figure 4-8. Forest plot for angle of peak torque assessed during 60°/sec concentric contraction

4.5.5 Flexibility

4.5.5.1 Passive straight leg raise

Data for all studies which examined the passive straight leg raise can be found in Appendix II Table 9.

Meta-analysis. Quantitative analysis of the passive straight leg raise (204, 206, 240, 242) revealed significantly reduced range of motion in previously injured legs compared to the uninjured contralateral leg. A large effect was found within 10 days (effect size, -1.12; 95%CI, -1.76 to -0.48; I^2 , 81%), a moderate effect between 10-20 days (effect size, -0.74; 95%CI, -1.38 to -0.09; I^2 , 76%), and a small effect between 20-30 days (effect size, -0.40; 95%CI, --0.78 to -0.03; I^2 , 4%) since the time of injury, with no significant effect found at 40 days or more since the time of injury (Figure 4-9). Meta-regression analysis (Figure 4-10) revealed a significant effect for time since injury (intercept, -0.81, $p < 0.0001$; coefficient, 0.006, $p = 0.019$), indicating that the magnitude of the range of motion deficit deceases with increasing time from injury.

4.5.5.2 Passive knee extension

Data for all studies which examined the passive knee extension can be found in Appendix II Table 10.

Meta-analysis. No significant differences were found for the passive knee extension measure at either time-point subgroup analysed (<10 days and 20-30 days post injury; Figure 4-11a, b).

Best evidence synthesis. A subset of the passive knee extension (insufficient data for subgroup meta-analysis, unable to be pooled with acute data) showed conflicting evidence across the three studies (221-223) that conducted this assessment post return to play.

4.5.5.3 Active knee extension

Data for all studies which examined the active knee extension can be found in Appendix II Table 10.

Meta-analysis. No significant differences were found for the passive knee extension measure at either time-point subgroup analysed (<10 days, 10-30 days, and >180 days post injury; Figure 4-11c, d, e).

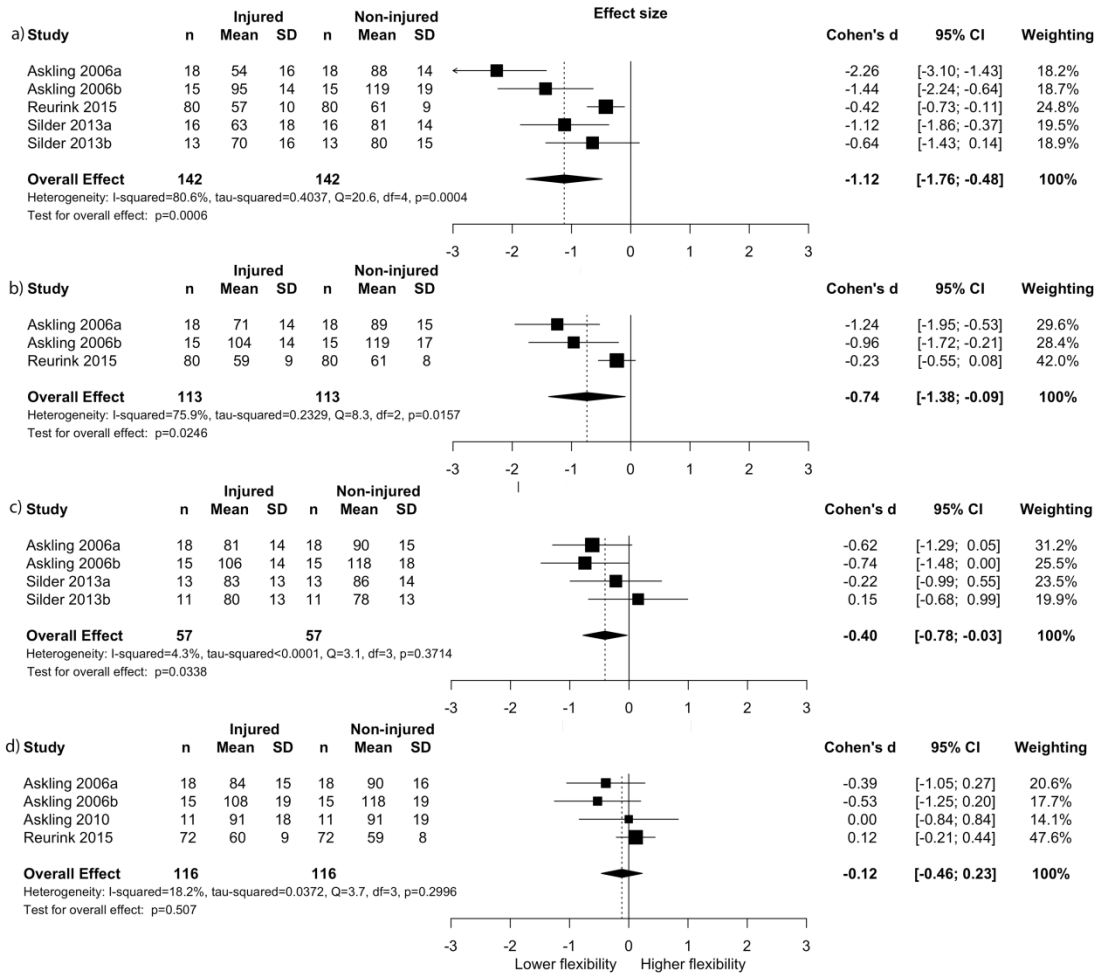

Figure 4-9. Forest plot of the passive straight leg raise at a) <10 days post injury, b) 10 days post injury, c) 21-30 days post injury, and d) >40 days post injury. Note that one study (204) had two subgroups, a, Progressive agility and trunk stabilisation rehabilitation protocol (PATS); b, Progressive running and eccentric strengthening rehabilitation protocol (PRES).

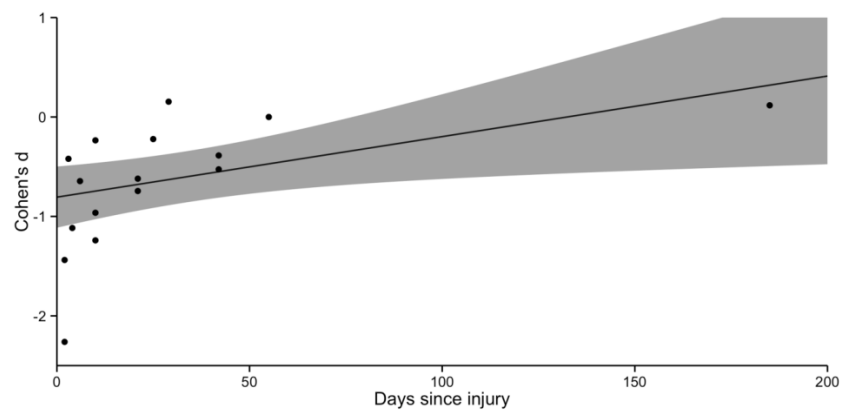

Figure 4-10. Meta-regression plot (with 95%CI) for the passive straight leg raise. Intercept, -0.81, p <0.0001; coefficient, 0.006, p = 0.019.

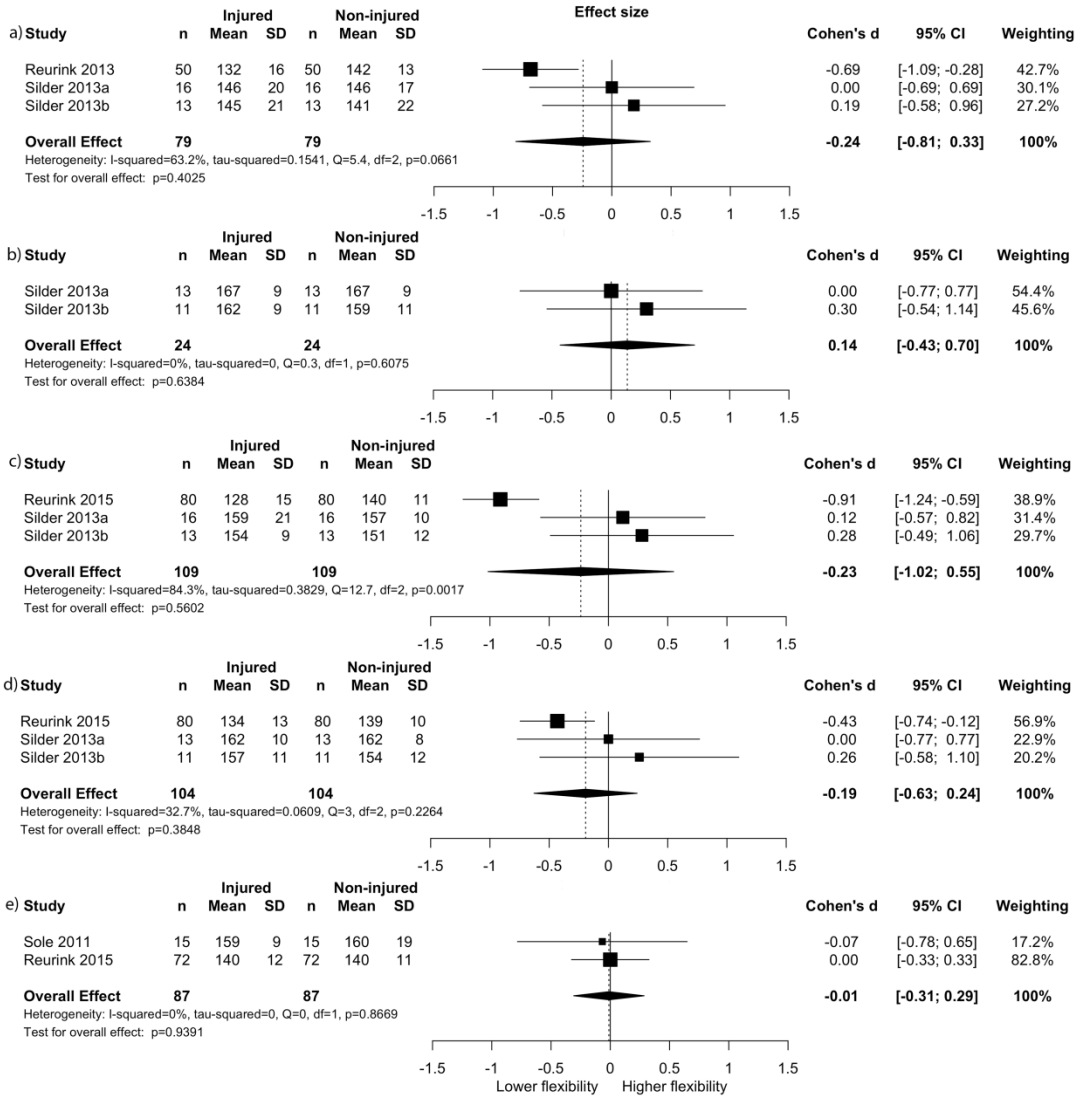

Figure 4-11. Forest plot for the knee extension assessments of range of motion at a) passive, <10 days post injury, b) passive, 20-30 days post injury, c) active, <10 days post injury, d) active, 10-30 days post injury, and e) active, >100 days post injury. Note that one study (204) had two subgroups, a, PATS; b, PRES.

4.5.5.4 Active straight leg raise

Data for all studies which examined the active straight leg raise can be found in Appendix II Table 9.

Best evidence synthesis. Conflicting evidence was found for deficits in the active straight leg raise (220, 240). Of note, the one study (240) which did find deficits in previously injured legs performed the active straight leg raise in a rapid manner (Askling-H test) and as

such this study could not be appropriately pooled with the other data for meta-analysis purposes.

4.5.5.5 Sit and reach

Best evidence synthesis. No evidence for differences in the sit and reach were found between healthy and previously injured participants (135, 238).

4.6 Discussion

Our systematic review revealed that after hamstring strain, isometric strength and passive straight leg raise deficits normalised within 20-50 days. Deficits at or after return to play, if they did exist, manifested during dynamic strength measures (eccentric and concentric strength and their associated H:Q strength ratios).

We only included research articles that contained data from participants who had previously sustained a HSI (between 2 and 690 days prior). As a result, we cannot determine whether the reported deficits were the cause of injury or the result of injury. Given the increased risk of future HSI in those with an injury history (199-202), the characteristics that exist in these legs should be given consideration by the clinicians responsible for rehabilitation and clearance to return to play.

4.6.1 Strength and flexibility deficits after hamstring injury

Conventional rehabilitation practice traditionally focuses on restoring isometric strength and range of motion (246). The meta-analysis revealed that deficits in long length (hip, 0°; knee, 0-15°) isometric strength and the passive straight leg raise are resolved 20-50 days post injury. This provides support for the use of the passive straight leg raise and isometric strength measures during rehabilitation (246). Furthermore, deficits in isometric strength and range of motion (as measured by the active knee extension test) just after return to play are independent predictors of re-injury (247), suggesting that these variables likely also have value in criteria based rehabilitation progressions. However, where evidence of deficits were found beyond return to play, these were during measures of dynamic strength.

The evidence supporting deficits in eccentric strength in those with prior HSI is mixed (35, 37, 135, 143, 211, 212, 214, 216-218, 238, 244). Lower levels of eccentric hamstring strength are proposed to increase the likelihood that the demands of high force musculotendinous lengthening, such as during the terminal swing phase of running, exceeds the mechanical limits of the tissue (248). It may be that lower eccentric strength in previously

injured hamstrings is at least partly responsible for the greater risk of recurrent hamstring strain (249).

Other measures of dynamic strength, including concentric strength (35, 135, 209, 211, 212, 215, 236-239, 241, 245) and both conventional (135, 209, 211, 212, 214, 215, 218, 236, 241, 244, 245) and functional (135, 211, 212, 214, 218, 236, 238, 239, 244) H:Q strength ratios also show conflicting findings, with measures at some testing velocities showing lower strength in previously injured legs, but others showing no differences. The reasons for these discrepancies are unclear, but may be due to inherent differences in groups studied, and/or methodological issues. For example, studies which included females tended to observe slightly higher strength in previously injured legs (244, 245). Insufficient data was available to assess this observation via regression analysis, thus more research is needed to investigate any potential gender-specific responses to HSI. The particulars of the rehabilitation performed could also explain disparate findings, as differing rehabilitation strategies would result in differing adaptations. Rehabilitation was rarely controlled in the included studies, suggesting more studies should aim to control rehabilitation to limit this potential confounder.

4.6.2 Mechanisms that may explain long-term dynamic muscle strength deficits

There is the possibility that chronic deficits in dynamic strength in previously hamstring-strain injured legs is a downstream outcome of prolonged neuromuscular inhibition (210). Reduced activation of previously injured hamstrings has been associated with maximal eccentric contractions (34-36, 135), particularly at long muscle lengths (35, 135). What remains to be seen, however, is whether or not these deficits are associated with increased risk of injury or re-injury, and what the most appropriate intervention is to ameliorate these deficits. However, activation deficits do not occur during concentric contractions (35, 135), thus further research is needed to understand why dynamic strength deficits tend to persist beyond return to play.

4.6.3 Clinical implications

The data presented in this review have implications for practitioners who are required to rehabilitate and return athletes to play following HSIs. The appendix results (Appendix II) tables provide practitioners a detailed resource of data for almost all strength and flexibility measures that have been assessed in athletes with a prior HSI. These data can be used to compare individual athlete/patient data. It should also enable practitioners to select measures to monitor in their injured athletes which are known to be in deficit despite ‘successful’ return to play. The presented evidence justifies the use of the passive straight leg raise and isometric

strength measures to monitor progression through rehabilitation, whilst additional measures of dynamic strength may have more value at and after return to play.

In addition, the present review would also question the use of commonly recommended (248, 250) and employed markers for successful rehabilitation, such as knee flexor angle of peak torque. The use of angle of peak knee flexor torque, particularly during concentric contraction, in athletes with prior HSI has been popularised following the seminal paper (241), however, the ensuing evidence is generally conflicting (209, 214, 236, 239) suggesting that the value of this measure should be questioned.

4.6.4 Limitations

The primary limitation of this review is that the retrospective nature of the data makes it impossible to determine if deficits are the cause or result of injury. For example, eccentric strength deficits could be the result of uncorrected strength deficiency that may have caused injury, as higher levels of eccentric strength and eccentric training are associated with a reduction in new and recurrent HSI (247, 251, 252). Furthermore, the majority of the included studies did not control rehabilitation, and this introduces another potential source of bias. For example, a study in which participants focused heavily on eccentric exercise as part of rehabilitation may show no evidence of significant eccentric strength deficits post HSI. Consequently, the effect of these interventions on strength and flexibility outcomes remains an area for future research. Ideally, researchers should control rehabilitation to minimise confounding, and where this is not possible, collect and report details of rehabilitation protocols. Inconsistent time from injury until testing between studies also introduces bias. We analysed data in time-bands and performed meta-regression analysis where possible to assess and adjust for this potential confounder, but also acknowledge that this approach was limited by within study variability, variability between studies within the time-band subgroups, and insufficient data for regression analysis. Future research should investigate the effect of time since injury on deficits, particularly prior to return to play, as strength and flexibility appear to change rapidly during this period.

One of the difficulties of this review was the numerous methods employed by different studies to assess a given parameter. For strength testing, it appeared that lower isokinetic velocities ($\leq$60°/sec) were the most sensitive to deficits, however there is insufficient data at higher velocities to draw definitive conclusions. Similarly, a number of different measures of flexibility (passive (204, 206, 217, 240) and active (220, 240) straight leg raise, passive (204, 221-223) and active knee extension (135, 204), sit and reach test (135, 238)) have been assessed

in previously injured athletes, with inconsistent findings amongst studies. Indeed, within each variable, the meta-analysis revealed significant heterogeneity as determined by the I^2 statistic in certain measures, particularly in the initial days following injury.

To address these issues as far as possible, we performed sensitivity analysis (Appendix II Table 11) to examine the influence of individual studies on effect estimates and heterogeneity where moderate (≥30%) heterogeneity (58) may have been present. Whilst high heterogeneity often impairs the validity of synthesised data, the low number of studies in many of these subgroups precludes confidence in the precision in these I^2 estimates, suggesting more studies are needed to properly interpret heterogeneity estimates. These studies should also take care to accurately describe diagnostic procedures, injury severity and other lower-limb injuries likely to confound results. The data reported in this review may also have limited application to female athletes, as majority of the data was obtained from male only or predominately male cohorts. We acknowledge that the search strategy may not have captured all relevant literature. However, reference list searching and citation tracking was also performed to enhance article retrieval.

4.7 Conclusion

In conclusion, the meta-analysis found that deficits in isometric strength and flexibility (as measured by the passive straight leg raise) resolve within 20-50 days following HSI. Deficits that were present beyond return to play were found for dynamic measures of strength (concentric and eccentric strength, and conventional and functional H:Q strength ratios). This evidence suggests that clinicians monitor isometric strength and the passive straight leg raise throughout rehabilitation, whilst dynamic measures of strength may hold more value at/after return to play. Furthermore, it may behove clinicians and patients to continue rehabilitation after return to play.

4.8 Supplementary data

The following section contains information that is pertinent to this thesis, but was removed from the manuscript during the peer-review process at the direction of the editor and reviewers. One of the aims of this thesis was to explore the relationship between prior HSI and ACL injury. Knee joint loading is multi-planar, thus understanding if other lower-limb muscles or multi-planar movements are examined post-HSI is important information to determine what further work needs to be done to better study an association between prior HSI and future ACL injury. Based on this, a secondary aim of this paper was to determine the breadth of data collected in individuals following HSI. Supplementary Table 4-1 provides a summary of measures taken following HSI, not limited to strength and flexibility as in the manuscript.

This data provides evidence that studies typically focus on the function (i.e. strength, flexibility, activation) and structure (i.e. architecture and morphology) of the hamstring muscle group. With the exception of quadriceps strength, little consideration is given to other lower-limb muscles. In addition to this, multi-planar loading is rarely considered. Three-dimensional loading is assessed during biomechanical assessments, but these have been thus far limited to running (209, 214, 253), which has vastly different multi-plane knee joint loading patterns than knee-joint injurious manoeuvres such as sidestep cutting (69). Consequently, further consideration of other lower-limb muscles during tasks that involve multi-planar knee loading is necessary to better understand the appropriate next steps for exploring the relationship between prior HSI and ACL injury.

Supplementary Table 4-1. Best evidence synthesis data for all major categories of outcome variables assessed in individuals with a prior hamstring strain injury.

Variable	Testing method	No. of studies	Consistency (%)			Quality (mean ± SD)	Level of evidence of difference
			Decrease	No change	Increase		
BFLH EMG eccentric contraction	Seated isokinetic	4	100	0	0	75 ± 6.25	Strong
Knee flexor eccentric strength[#]	Seated isokinetic	9	77.8	22.2	0	66.67 ± 8.84	Strong
Knee flexor eccentric strength[#]	Nordic hamstring exercise	2	100	0	0	75 ± 8.84	Moderate
Knee flexor eccentric rate of torque development	Seated isokinetic	1	100	0	0	75	Moderate
Knee flexor eccentric impulse	Seated isokinetic	1	100	0	0	75	Moderate
BFLH Fascicle length	Two dimensional ultrasound	1	100	0	0	81.25	Moderate
BFLH Pennation angle	Two dimensional ultrasound	1	0	0	100	81.25	Moderate
Horizontal force	Running	2	100	0	0	62.5 ± 8.84	Moderate
Knee flexor eccentric work	Seated isokinetic	1	100	0	0	68.75	Limited
Posture	Lumbar lordosis	1	0	0	100	50	Limited
Knee flexor fatigueability	Single-leg hamstring bridge	1	100	0	0	62.25	Limited
Biceps femoris tissue strain	Magnetic resonance imaging	1	100	0	0	62.50	Limited
Peak hip flexion angle	Running	1	100	0	0	68.75	Limited
Conventional H:Q	Seated isokinetic	12	8.3	91.7	0	66.15 ± 6.77	Conflicting
Functional H:Q	Seated isokinetic	7	71.4	28.6	0	67.86 ± 6.68	Conflicting
Knee flexor concentric strength[#]	Seated isokinetic	14	50	35.7	14.3	69.20 ± 8.30	Conflicting
Knee flexor eccentric angle of peak torque	Seated isokinetic	2	0	50	50	68.75 ± 0.00	Conflicting
Knee flexor concentric angle of peak torque	Seated isokinetic	5	0	80	20	70.00 ± 6.85	Conflicting

Knee flexor isometric Strength	Prone position using a dynamometer	2	50	50	0	68.75 ± 17.68	Conflicting
Knee flexor concentric work	Seated isokinetic	2	50	50	0	75 ± 8.84	Conflicting
Hamstring flexibility[#]	Passive straight leg raise	3	66.7	33.3	0	66.67 ± 9.55	Conflicting
Hamstring flexibility	Active straight leg raise	2	50	50	0	59.38 ± 13.26	Conflicting
Hamstring flexibility	Passive knee extension	3	66.7	33.3	0	68.75 ± 0	Conflicting
Biceps femoris long head volume	Magnetic resonance imaging	2	0	50	50	75 ± 8.84	Conflicting
Biceps femoris short head volume	Magnetic resonance imaging	2	0	50	50	75 ± 8.84	Conflicting
Hamstring tendon volume	Magnetic resonance imaging	3	0	66.7	33.3	75 ± 6.25	Conflicting
BFLH EMG activity during concentric contraction	Seated isokinetic	2	0	100	0	75 ± 8.84	None
Hamstring flexibility	Active knee extension	1	0	100	0	68.75	None
Hamstring flexibility	Sit and reach	2	0	100	0	68.75	None
BFLH Muscle Thickness	Two dimensional ultrasound	1	0	100	0	81.25	None
Semitendinosus volume	Magnetic resonance imaging	1	0	100	0	81.25	None
Motor control	Movement Discrimination	1	0	100	0	68.75	None

BFLH, biceps femoris long head; EMG, electromyography; H:Q, hamstrings to quadriceps strength ratio; SD, standard deviation.
[#] This category contained studies that did not include appropriate statistical analysis for inclusion in this table, but contained data that was included in the meta-analysis.

Chapter 5 – Study 2: Non-knee-spanning muscles contribute to tibiofemoral shear as well as valgus and rotational joint reaction moments during unanticipated sidestep cutting

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5.1 Linking paragraph

Chapter 4 demonstrated that hamstring muscle strength is impaired following hamstring strain injury (HSI). Given the previously described importance of the hamstring muscle group in unloading the anterior cruciate ligament (ACL), this finding strengthens the rationale for further investigating the relationship between prior HSI and ACL injury. However, despite consistent evidence demonstrating the importance of the hamstrings in unloading the ACL (as reviewed in Chapter 2), studies investigating the influence of the hamstrings during potentially injurious manoeuvres is limited. Additionally, little consideration has been given to non-knee-spanning lower-limb muscles, despite evidence demonstrating the non-knee-spanning muscles can contribute substantially to knee joint loading. Subsequently, Chapter 5 focused on how lower-limb muscles contribute to the surrogate markers of ACL load. This work aimed to investigate the function of the hamstrings under practically relevant conditions (i.e. during a potentially injurious manoeuvre) and to describe their contribution relative to other lower-limb muscles. This data is needed before further investigations attempt to determine the influence of prior HSI on lower-limb muscle function in relation to knee joint loading, and may guide appropriate targets for improvements to strength or activation of specific muscles in interventions aiming to reduce ACL injury risk.

5.2 Abstract

Anterior cruciate ligament injuries are a burdensome condition due to potential surgical requirements and increased risk of long term debilitation. Previous studies indicate that muscle forces play an important role in the development of ligamentous loading, yet these studies have typically used cadaveric models considering only the knee-spanning quadriceps, hamstrings and gastrocnemius muscle groups. Using a musculoskeletal modelling approach, we investigated how lower-limb muscles produce and oppose key tibiofemoral reaction forces and moments during the weight acceptance phase of unanticipated sidestep cutting. Muscles capable of opposing (or controlling the magnitude of) the anterior shear force and the external valgus moment at the knee are thought to be have the greatest potential for protecting the ACL from injury. We found the best muscles for generating posterior shear to be the soleus, biceps femoris long head and medial hamstrings, providing up to 173N, 111N and 77N of force directly opposing the anterior shear force. The valgus moment was primarily opposed by the gluteus medius, gluteus maximus and piriformis, with these muscles providing contributions of up to 32Nm, 19Nm and 21Nm towards a knee varus moment, respectively. Our findings highlight key muscle targets for anterior cruciate ligament preventative and rehabilitative interventions.

5.3 Introduction

Anterior cruciate ligament (ACL) injury is a burdensome condition due to potential surgical requirements, substantial convalescence and rehabilitation time (2), and associated financial costs to individuals and the healthcare system (3). ACL injury has also been shown to be associated with an increased risk of early onset knee osteoarthritis, especially if accompanied by meniscal injury (254). Consequently, knowledge regarding the mechanical factors related to ACL injury and injury risk is needed to develop effective prophylactic strategies.

Whilst the primary role of the ACL is to resist anterior translation of the tibia relative to the femur (21), both cadaveric and modelling studies have shown that frontal and transverse plane knee mechanics can also influence ACL loading (17-20). In the frontal plane, a greater 'external' knee valgus or varus moment has the potential to increase load on the ACL (17, 20). However, knee valgus has been reported to be the more common mechanism of injury in video analysis studies (9, 10, 15). In the transverse plane, an 'external' moment causing internal rotation of the tibia with respect to the femur has been found to expose the ACL to higher loads than an 'external' moment causing external rotation of the tibia with respect to the femur (17, 20). Moreover, non-sagittal plane knee joint moments have been shown to have the greatest influence on ACL loading when they occur simultaneously and especially in conjunction with an anterior shear force (17, 19, 20, 22). A better understanding regarding the development of these critical knee joint loads could therefore be beneficial for improving ACL preventative and rehabilitative strategies.

Muscles produce forces that can cause and oppose these critical knee joint loads. For example, the quadriceps generates an anterior tibiofemoral shear force which is directly opposed by the ACL (27). In contrast, the hamstrings have the potential to mitigate anterior tibiofemoral shear forces thereby working with the ACL to control the amount of anterior translation at the knee joint (27, 28). Despite the amount of research completed to date, existing knowledge regarding biomechanical variables associated with high loading of the ACL is still quite limited. No studies have investigated which muscles contribute most substantially towards critical knee joint loads during high injury risk tasks such as unanticipated cutting. Furthermore, through "dynamic coupling", any muscle in the body can potentially induce an acceleration of any segment in the body (38). For example, it is possible that certain hip muscles can influence knee joint loads during rapid change-of-direction tasks. Ignoring the role of the hip muscles may mean that some valuable information that could be used to guide preventative and rehabilitative interventions has been overlooked.

Musculoskeletal modelling enables the cause-effect relationships between muscle forces and joint loads during high injury risk tasks to be evaluated (77). Subsequently, the purpose of this study was to investigate the role of the major lower-limb muscles on key tibiofemoral loading parameters associated with ACL injury during an unanticipated sidestep cut. Specifically, we used a computational musculoskeletal modelling approach to predict lower-limb muscle contributions to the knee joint anteroposterior shear force as well as the frontal and transverse plane moments. Our primary interest was to identify which muscles have the greatest capacity to control/minimise the anterior shear force as well as the knee valgus and internal rotation moments, as the function of such muscles could then be targeted in ACL prevention programs.

5.4 Methods

5.4.1 Participants

Eight recreationally active healthy males (age: 27 ± 3.8 years; height: 1.77 ± 0.09m; mass: 77.6 ± 12.8kg) volunteered to participate in this study. All participants had no current or previous musculoskeletal injury likely to influence their ability to perform the required tasks. All participants provided written informed consent to participate in the study. Ethical approval was granted by the Australian Catholic University human research ethics committee (approval number: 2015-11H), and the study was carried out in accordance with the approved guidelines.

5.4.2 Instrumentation

Three-dimensional marker trajectories were collected at 200Hz using a nine camera motion analysis system (VICON, Oxford Metrics Ltd., Oxford, United Kingdom). Ground reaction forces (GRF) were collected via two ground-embedded force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) sampling at 1000Hz. Surface electromyographic (EMG) data were collected at 1000Hz from 10 lower-limb muscles on the dominant leg (defined as the kicking leg; right side for all participants) via two wireless EMG systems (Noraxon, Arizona, USA; Myon, Schwarzenberg, Switzerland).

5.4.3 Procedures

All participants were barefoot during the completion of all tasks, which allowed exposure of the foot for marker placement and kept the foot-ground interaction consistent across all participants. The skin was prepared for surface EMG collection by shaving, abrasion and sterilisation. Circular bipolar pre-gelled Ag/AgCl electrodes (inter-electrode distance of 2cm) were then placed on the vastus lateralis and medialis, rectus femoris, biceps femoris, medial

hamstrings, medial and lateral gastrocnemius, soleus, tibialis anterior and peroneus longus muscles in accordance with Surface Electromyography for the Non-Invasive Assessment of Muscle (SENIAM) guidelines (152). EMG-time traces during forceful isometric contractions were visually inspected to verify the correct placement of the electrodes and to inspect for cross-talk. Forty-three 14 mm retroreflective markers were affixed to various anatomical locations on the torso (sternum, the spinous process of the 7th cervical vertebra, the spinous process of a mid-thoracic vertebra, the tip of each acromion), pelvis (anterior and posterior superior iliac spines), upper-limbs (medial and lateral elbow and distal radius and ulna) and lower-limbs (medial and lateral femoral epicondyles, medial and lateral malleoli, first and fifth metatarsophalangeal joints, calcaneus and three additional markers on each shank and thigh) of each participant.

Each participant completed two unanticipated change-of-direction tasks on their dominant leg. Participants were required to perform two single-leg hops for a standardised distance of 1.35m, and then as quickly as possible cut to the left (45º sidestep cut) or to the right (45º crossover cut) upon landing from the second hop. We used a hopping approach based on prior research (153) because it allows speed and foot placement on the force plate to be well controlled across participants relative to a running approach. The direction of travel was randomly dictated by a set of timing gates (Smartspeed, Fusion Sport, Australia) that delivered a light signal ~450ms prior to initial contact on the force plates. Floor markings were used to indicate the starting point, the hop landing targets and the required 45º angle from the force plates for the cutting direction. A successful trial required that the participant completed the task correctly with the entire foot landing within the force plate. This protocol produced approach velocities (2.24 ± 0.15 m/s) and cutting angles (41 ± 2º) that were consistent with characteristics reported during ACL injuries (151). Note that we only analysed sidestep cuts in this investigation, as this task has been most commonly associated with injury to the ACL (9, 10, 14, 151).

5.4.4 Data processing

Marker trajectories were low-pass filtered using a zero-lag, 4th order Butterworth filter with a cut-off frequency of 8Hz. This cut-off frequency was determined via a residual analysis. GRFs were filtered using the same filter and cut-off frequency as the marker data based on published recommendations (154). EMG data were corrected for offset, high-pass filtered (20Hz), full-wave rectified and low-pass filtered (6Hz) using a zero-lag, 4th order Butterworth filter to obtain a linear envelope. EMG data were normalised to the peak amplitude obtained in each trial.

5.4.5 Musculoskeletal modelling

A 37 degree of freedom (DOF) full-body musculoskeletal model, with 80 musculotendon actuators (lower body) and 17 torque actuators (upper body) (76), was used to perform the musculoskeletal simulations in OpenSim (77). Each hip was modelled as a 3-DOF ball and socket. Each knee was modelled as a 1-DOF hinge, with other rotational (valgus/varus and internal/external rotation) and translational (anteroposterior and superior-inferior) movements constrained to change as a function of the knee flexion angle (157). A pin joint was used to represent the ankle (talocrural) joint. The head-trunk segment was modelled as a single rigid segment, articulating with the pelvis via a 3-DOF ball and socket joint. Each upper limb was characterised by a 3-DOF ball and socket shoulder joint and single-DOF elbow and radioulnar joints. The subtalar, metatarsophalangeal, and wrist joints were locked (76). The generic model was scaled to each participant's individual anthropometry as determined during a static trial. An inverse kinematics algorithm was used to calculate joint angles by means of a least-squares optimisation that minimised the difference between model and experimental marker positions (161). Inverse dynamics was used to obtain the joint moments acting about each modelled DOF. Muscle forces were obtained via a static optimisation algorithm, which decomposed the joint moments into individual muscle forces by minimising the sum of muscle activations squared, taking into account the physiological force-length-velocity properties (169) of the musculotendinous units. This method of muscle force estimation is computationally efficient and has been used to predict muscle forces in similar high-impact movements (101, 149, 170). Note that the maximum isometric force of each actuator was increased 3-fold from the standard model, similar to another study that investigated high-impact manoeuvres (170).

The measured GRFs were decomposed into individual muscular contributions by means of a pseudo-inverse-based approach (149, 155, 156). Each muscle's contribution to the joint reaction forces and moments about the knee were then computed by applying each muscle's force and contribution to the GRF in isolation and resolving the dynamical equations of motion. The knee joint reaction forces and moments represent the forces and moments that the knee joint experiences as a consequence of all motions and forces in the model, including muscles and other actuators. These parameters differ somewhat from the inverse dynamics-based outputs used with the static optimisation algorithm to calculate muscle forces.

5.4.6 Outcome variables

Outcome variables of interest were each muscle's contribution to the tibiofemoral anteroposterior shear joint reaction force as well as the frontal and transverse plane joint

reaction moments, as these variables have been shown to be associated with higher ACL loads and/or injury (17, 18). Since ACL injuries occur promptly after initial contact (10), we limited our analysis to the weight acceptance phase (period of stance from foot-strike to the first trough in the raw vertical GRF) as per previous research (69, 146). Muscular contributions were grouped according to function consistent with a prior approach (107), except where these muscles had opposing effects on the key tibiofemoral loading parameters. For example, the biceps femoris long head and medial hamstrings (i.e. semimembranosus and semitendinosus) have opposing transverse plane actions at the knee, hence the biarticular hamstrings were not grouped together (see Appendix II Table 12 for all functional groupings). Note that we only report on major muscle groups, and did not report on any muscle that was not found to make a meaningful contribution to any of the three key knee reaction forces or moments (see Rajagopal et al. (76) for all musculotendinous actuators included in the model).

5.4.7 Validation and verification

To provide confidence in our simulations, we performed qualitative comparisons between the model-based predicted activations and experimental EMG data, accounting for appropriate physiological delays (~100ms) as per current recommendations (113). We obtained EMG data from experimental recordings collected in the present study and from available data in the literature (46, 147). Since these comparisons were conducted to assess how well the simulation replicated the coordination pattern observed experimentally, the normalised EMG data were averaged across participants and then renormalised to the peak amplitude of each muscle. The predicted activations were processed using the same normalisation procedure as the EMG data, prior to these comparisons. We also compared the time-varying characteristics of our experimental joint angles and inverse dynamics based joint moments to ensure they were within 2SD of prior published data (113). These qualitative comparisons were conducted across the entire stance phase because the weight acceptance phase was generally too short to allow any firm conclusions to be made about how well our model-based predicted data temporally matched experimental data as well as data obtained from the literature.

We quantitatively verified that our muscle-derived joint moments (computed from the predicted muscle forces and their respective moments arm) matched the experimentally measured joint moments (computed via inverse dynamics) by calculating the normalised root mean square error (nRMSE) and coefficient of determination (R^2). The nRMSE was calculated as:

$$\text{nRMSE}\ (\%) = 100 \times \frac{\sqrt{\frac{\sum_{i=1}^{n} (Experimental_i - Predicted_i)^2}{n}}}{\max(Experimental) - \min(Experimental)}$$

To verify the suitability of the foot-ground contact model, superposition errors between experimental and simulated GRFs were quantitatively evaluated via computation of the nRMSE and R^2. These data were reported as the median and interquartile range (IQR) due to non-normal distributions.

5.4.8 Data availability

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

5.5 Results

5.5.1 Validation

Muscle-derived joint moments showed excellent agreement with inverse dynamics based joint moments (R^2, 1.0, IQR, 1.0 to 1.0; nRMSE, 3.21 x 10^{-3}%, IQR, 1.5 x 10^{-3} to 1.1 x 10^{-2}%; Figure 5-1). The foot-ground contact model also showed acceptable results, with model-predicted GRFs in agreement with experimentally measured GRFs (R^2, 0.95, IQR, 0.92 to 0.97; nRMSE, 7.9%, IQR, 6.1 to 10%). Additionally, once appropriate physiological delays were taken into account (100ms corresponds to ~25% of stance phase), reasonable agreement was evident between the predicted muscle activations from the model and experimentally recorded EMG data obtained from the current study as well as prior literature (Figure 5-2).

5.5.2 Anteroposterior shear joint reaction force

The net anteroposterior shear force was characterised by an anterior shear force of 218N at initial contact, which gradually declined until switching to a posterior shear force at 46% of the weight acceptance phase (Figure 5-3A and B). The greatest contributors to the posterior shear force were the biarticular hamstrings and soleus. The contribution of each of these muscles increased throughout weight acceptance, peaking at 173N, 111N, and 77N for the soleus, biceps femoris long head and medial hamstrings, respectively. The anterior shear force was primarily produced by the quadriceps and gastrocnemius muscle groups. The vasti's contribution increased throughout weight acceptance, peaking at 225N, whilst contributions from the rectus femoris and lateral gastrocnemius peaked at initial contact at 83N and 38N, respectively. The medial gastrocnemius peaked at 84N at 5% of weight acceptance, and remained at around 60N for the majority of the remainder weight acceptance. The non-knee-

spanning ankle dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), adductors and gluteus maximus also contributed 50-60N during mid-weight acceptance. The shift to a net posterior shear force at 46% of weight acceptance was mainly explained by a decline in the contribution from the gastrocnemius towards anterior shear, and an increase in the contribution from the biarticular hamstrings and soleus towards posterior shear.

5.5.3 Frontal plane joint reaction moment (varus/valgus)

A varus knee joint reaction moment (peak of 25Nm) was present for the first 72% of weight acceptance, whereas a valgus knee joint reaction moment (peak of 12Nm) was present for the remaining portion (Figure 5-3C and D). Throughout weight acceptance, the gluteal muscles had the greatest capacity to oppose the valgus moment. The gluteus medius produced the largest varus moment (ranging from 23-32Nm across weight acceptance). Substantial contributions were also made by the piriformis (7-21Nm) and gluteus maximus (9-19Nm). The transition to a valgus knee joint reaction moment was driven by decreasing contributions from the gluteals, piriformis and adductors towards a varus moment, and increasing contributions from the vasti (up to 31Nm), soleus (up to 10Nm) and biceps femoris long head (up to 4Nm) towards a valgus moment.

5.5.4 Transverse plane joint reaction moment (internal/external rotation)

An external rotation knee joint reaction moment was present throughout the entire weight acceptance period (Figure 5-3E and F). The external rotation moment was 1-2Nm for the first quarter of weight acceptance. It progressively increased during the second half of weight acceptance, peaking at 25Nm. The dominant contributors towards this moment were the vasti (up to 23Nm) and soleus (up to 10Nm) muscles. The gluteus maximus (2-10Nm) and gluteus medius (4-5Nm) muscles had the greatest potential to oppose this moment (i.e. contribute to an internal rotation knee joint reaction moment) throughout weight acceptance.

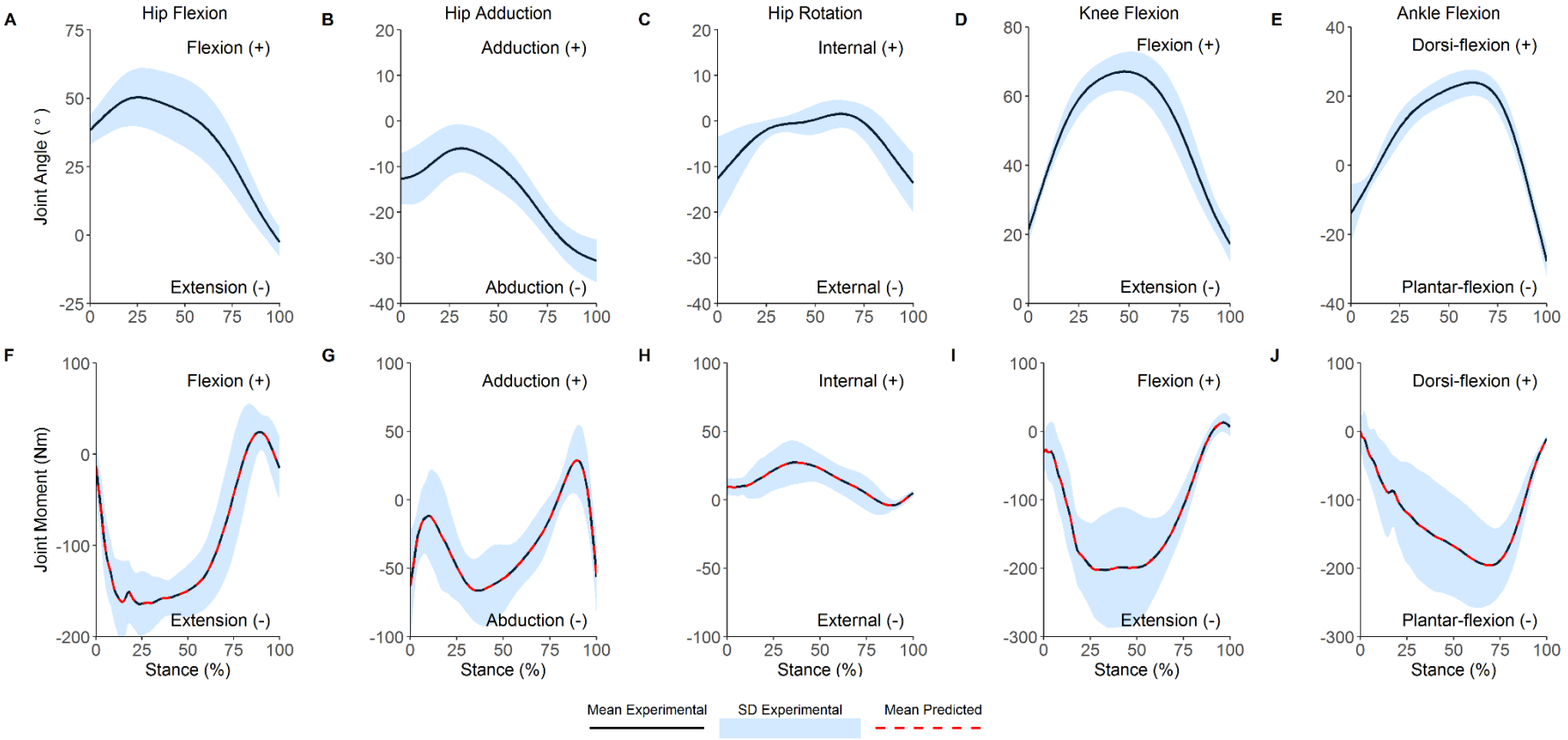

Figure 5-1. Joint angles and joint moments during the stance phase of the 45º unanticipated sidestep cut. Top row, mean (black line) and SD (blue shaded) joint angles; bottom row, experimental (mean, black line; SD, shaded blue) and predicted (red dotted) lower-limb joint moments.

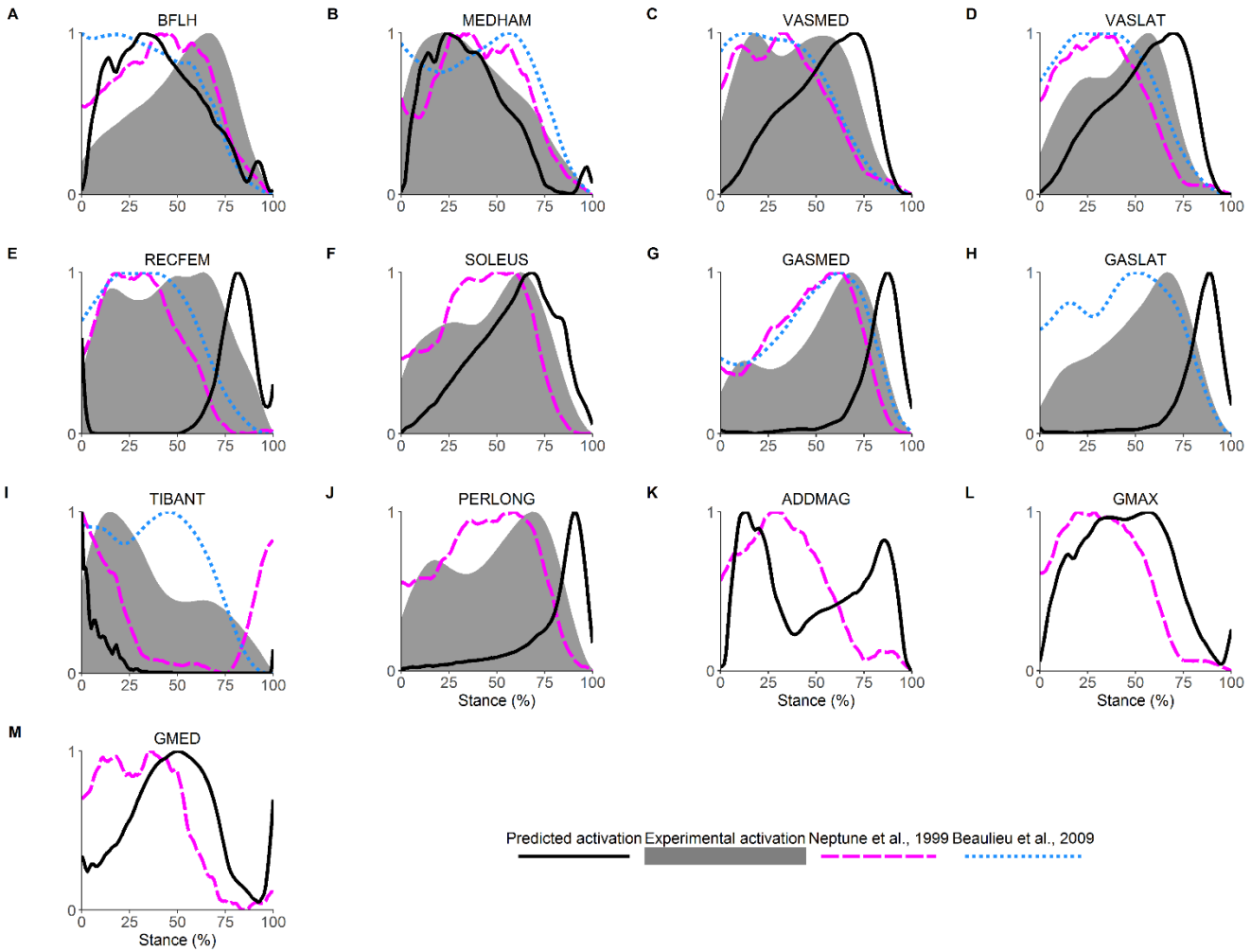

Figure 5-2. Comparison of predicted (black line) and experimental activations (grey shaded) from the current data during the stance phase of the 45º unanticipated sidestep cut. Literature reference activations, magenta dashed line, Neptune et al., 1999 (46); blue dashed line, Beaulieu et al., 2009 (147). Panels, A, biceps femoris long head; B, medial hamstrings (semimembranosus and semitendinosus); C, vastus medialis; D, vastus lateralis; E, rectus femoris; F, soleus; G, gastrocnemius medialis; H, gastrocnemius lateralis; I, tibialis anterior; J, peroneus longus; K, adductor magnus; L, gluteus maximus; M, gluteus medius.

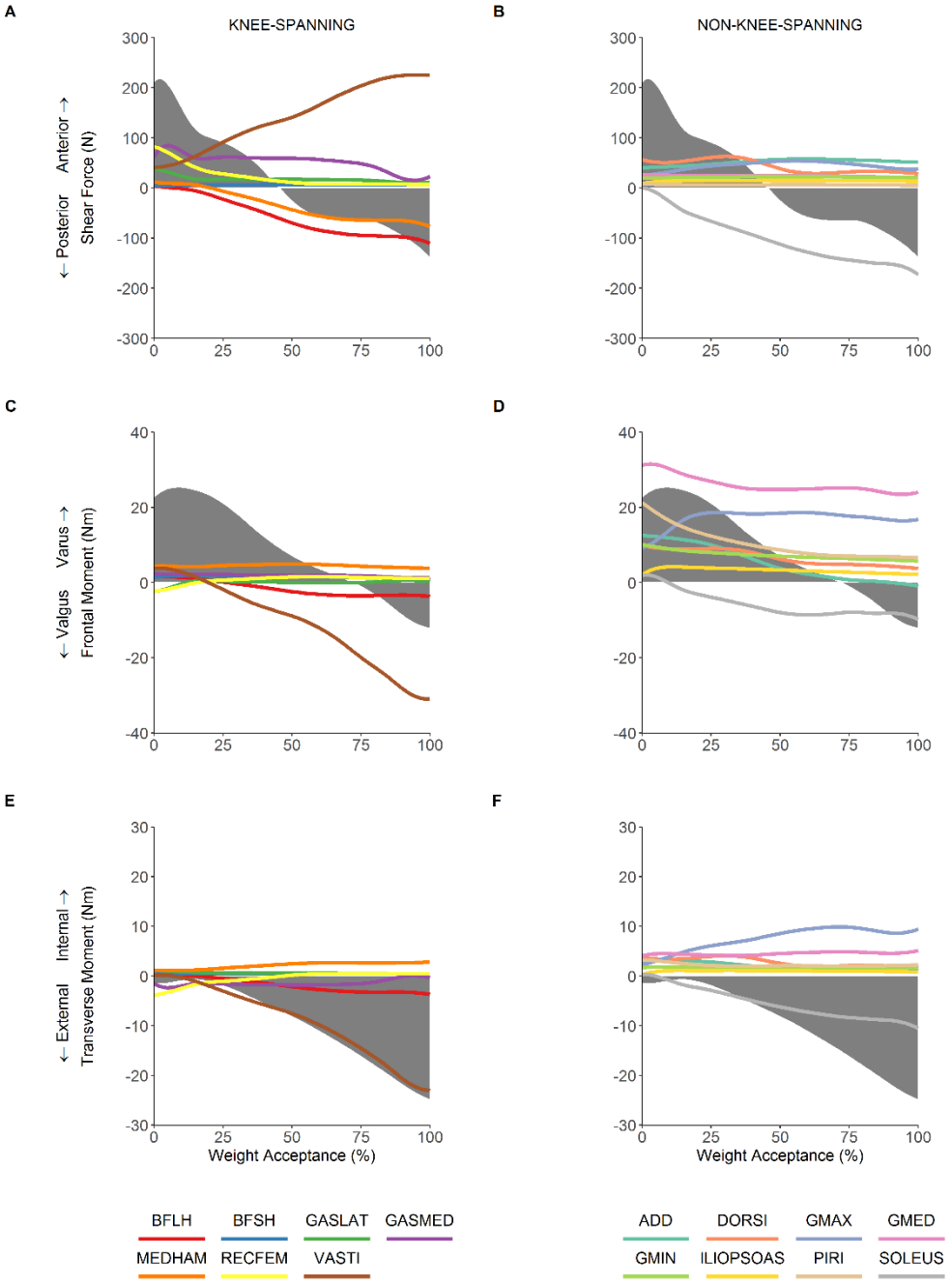

Figure 5-3. Muscular contributions to knee anteroposterior shear joint reaction force (row 1), frontal plane knee joint reaction varus/valgus moment (row 2) and transverse plane knee joint reaction internal/external rotation moment (row 3) during the weight acceptance phase of the 45° unanticipated sidestep cut. The first column (panels A, C and E) show knee-spanning muscles, the second column (panels B, D, and F) show non-knee-spanning muscles. Note that the shaded grey represents the experimental value (net value accounting for all forces) for each reaction load. BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOLEUS, soleus.

5.6 Discussion

This study has shown that both knee-spanning and non-knee-spanning muscles contribute to the tibiofemoral reaction forces and moments during the weight acceptance phase of a rapid unanticipated sidestep cut. Notably, we found the biarticular hamstrings and the soleus muscles to have the greatest potential to oppose the anterior shear reaction force, whilst the hip abductors (gluteus medius, gluteus maximus and piriformis) had the greatest potential to oppose the knee valgus reaction moment. To the authors' knowledge, no previous studies have calculated muscular contributions to knee joint loads during rapid change-of-direction manoeuvres.

The data reported in the present paper are largely consistent with prior literature. Experimental kinematics (Figure 5-1, top row) and inverse dynamics based joint moments (Figure 5-1, bottom row) were within 2SD of prior research investigating similar cutting tasks (153, 255, 256). Additionally, the predicted muscle activations showed reasonable agreement with EMG data for sidestep cutting obtained from the current study and the literature (46, 147). Whilst this consistency provides some evidence that our simulations were physiologically acceptable, the main focus of the present study concerned muscular contributions to the tibiofemoral anteroposterior shear reaction force as well as the frontal and transverse plane joint reaction moments. To our knowledge, only one study by Sritharan and colleagues (107) has reported comparable data. They computed the muscular contributions to the 'external' knee varus moment during gait. Note that Sritharan et al. (107) quantified the muscular contributions to the inverse-dynamics based joint moments, rather than the joint reaction forces/moments as we have reported here. Additionally, they did not include all of the muscles we have evaluated in the present study. Finally, they investigated walking, which has quite different biomechanical demands to sidestep cutting. Nevertheless, some consistent functional roles for key muscles are evident when comparing data from Sritharan et al. (107) with equivalent data from the present study. For example, we observed that the gluteal muscle group had the greatest potential to generate a varus knee joint reaction moment during the weight acceptance phase of sidestep cutting, i.e. these muscles opposed the net valgus knee joint reaction moment that occurred during the final 25% of weight acceptance (Figure 5-3D). Similarly, Sritharan et al. (107) found that the gluteus medius and gluteus maximus muscles were the major contributors to the 'external' knee varus moment during the stance phase of walking. They also found that the vasti and soleus were dominant contributors towards an 'external' knee valgus moment, which is consistent with the findings from the current study for cutting (Figure 5-3C and 3D).

5.6.1 Anteroposterior shear joint reaction force

The primary role of the ACL is to resist anterior tibial translation (21), and thus tibiofemoral shear has received much attention in the literature (17-19). The quadriceps and hamstring muscle groups are of particular interest in this respect due to their ability to induce anterior and posterior shear forces, respectively (128). We found that the vasti and biarticular hamstrings were indeed major contributors to anterior and posterior shear forces, respectively. However, our analysis provided insight into the critical role of other muscles, particularly the gastrocnemius and soleus, which appeared to have considerable yet opposing roles in the development of tibiofemoral shear force (Figure 5-3A and B). The opposing roles of the gastrocnemius and soleus muscles has been observed in previous research investigating contributions to trunk and leg segmental energy (257) as well as whole body sagittal plane angular momentum during gait (258). We have shown that the soleus tends to induce posterior shear reaction forces, whilst the gastrocnemius tends to induce anterior shear reaction forces at the tibiofemoral joint. Our results therefore suggest that the soleus and gastrocnemius represent ACL agonists and antagonists, respectively; an observation that is consistent with prior musculoskeletal modelling (101, 105) and in-vivo studies (119). In contrast to these findings, Morgan and colleagues (146) reported that the gastrocnemius plays a role in unloading the ACL by increasing joint compression and thereby resisting tibial translation (78). However, this assertion was based on a hypothetical explanation of elevated gastrocnemius forces observed in participants with low versus high estimated ACL loading. The role of joint compression is contentious, as animal models have shown that whilst joint compression may act to reduce anteroposterior translation, the direct influence on ACL loading may still be hazardous (81). Nevertheless, we accept that muscular contributions to knee joint compression could have potential implications for ACL loading, thus we have computed these values for completeness and have included the results as supplementary material for the interested reader (Appendix II Figure 1). In contrast, knee joint anterior shear force has consistently been associated with ACL loading (17, 19, 23-26), thus our cause-effect analysis showing that the gastrocnemius group induces anterior shear forces would suggest that the role of the gastrocnemius on its own is unlikely to be “protective”.

5.6.2 Frontal and transverse plane joint reaction moments

One of the most noteworthy findings in this study is that the gluteal muscle group is capable of generating a varus knee joint reaction moment, thus opposing (or controlling the magnitude of) the net valgus knee joint reaction moment during the final 25% of weight acceptance of sidestep

cutting. The gluteus medius provided the greatest contribution to the varus knee joint reaction moment for almost the entire weight acceptance phase, whilst other muscles (piriformis and gluteus maximus and minimus) also made appreciable contributions (Figure 5-3D). This result has implications for preventative and rehabilitative interventions, as both knee valgus loading (75) and lower hip abduction strength (133) have been prospectively associated with ACL injury. Additionally, knee valgus loading patterns have been observed during ACL injuries (9, 10, 15), and has been directly related to ACL loading (17, 19, 20). The gluteal muscles were also found to be the primary contributors to the internal rotation knee joint reaction moment (Figure 5-3F), which potentially increases loads on the ACL (17, 19, 22). However, the size of this contribution was relatively small (≤10Nm), and the tibiofemoral joint never experienced a net internal rotation reaction moment at any stage during the weight acceptance phase (Figure 5-3E and F). As sidestep cutting is typically associated with valgus loading (69), which is thought to be particularly relevant for non-contact injury mechanisms (10, 14), the function of the gluteal muscle group may be an important target for prevention programs aiming to reduce ACL injury risk. To our knowledge, no other study has demonstrated the importance of the gluteus medius (or the other hip abductor muscles) for opposing the knee valgus moment that occurs during sidestep cutting.

5.6.3 Simultaneous multi-direction loading

It is thought that loads on the ACL are greatest when the knee joint is exposed to an anterior shear force together with a valgus and an internal rotation moment (17, 19, 23). Whilst this specific combination of tibiofemoral reaction forces and moments was not observed to occur simultaneously in our data (Figure 5-3), muscular contributions must still be considered across multiple planes due to their potential to cause or oppose relevant joint reaction forces and moments. Whilst a valgus moment that occurs together with an internal rotation moment has the potential to increase load on the ACL (17, 19, 20, 22), none of the major contributors to a valgus knee joint reaction moment were also found to be major contributors to an internal rotation knee joint reaction moment (Figure 5-3C-F). The relative importance of non-sagittal loads to ACL loading is not universally accepted (259), whereas anterior and posterior shear forces have been consistently shown to load and unload the ACL, respectively (17-19, 23-26). Subsequently, appropriate muscular targets for interventions should be chosen primarily based on the magnitude of their contributions to anteroposterior shear force, with contributions to non-sagittal plane joint reaction moments perhaps a secondary consideration.

5.6.4 Key clinical implications

Based on the findings from this study, we suggest that injury prevention strategies should focus on optimising the function of the hamstring muscle group, as the biceps femoris long head and medial hamstrings were shown to be the two primary contributors to posterior shear during weight acceptance of sidestep cutting (Figure 5-3A). Additionally, these muscles induce opposite loading patterns in the frontal (Figure 5-3C) and transverse planes (Figure 5-3E), thus reducing the likelihood for combined unfavourable loading patterns to be generated. The function of the soleus would also seem important, due to this muscle's contribution to the posterior shear knee joint reaction force (Figure 5-3B), whilst also contributing to an external rotation knee joint reaction moment (Figure 5-3F). However, from a practical standpoint, the function of the soleus may be difficult to isolate from the gastrocnemius, a muscle group which we found to contribute to the anterior shear reaction force at the knee. Finally, the gluteal group, especially the gluteus medius and the piriformis muscles, were the dominant controllers of the valgus knee joint reaction moment (Figure 5-3D), and also made no meaningful contribution towards anterior shear and their contribution towards an internal rotation knee joint reaction moment was minimal. For these reasons, we consider training the function of the gluteus medius and piriformis muscles to be of high priority in ACL prevention programs.

5.6.5 Limitations

Whilst our study has revealed some novel insights, we acknowledge that there are some limitations to this work. One limitation is that the present study only involved a cohort of eight healthy recreationally active males. Further research should consider the influence of different populations such as females, specific athletic subgroups, and pathological populations. Additionally, participants were barefoot during the performance of the sidestep cut, which is not representative of many sports that involve footwear. There is the possibility that this may have resulted in an imposed foot-strike pattern for some participants, and a natural foot-strike pattern for others (260). However, we do not believe this influenced the conclusions of the study. The advantage of the barefoot condition was that it ensured a consistent foot-ground interaction across participants, and allowed exposure of the foot for marker placement.

Another limitation is that we did not compute ACL forces directly. Whilst including knee ligaments into the musculoskeletal model would have allowed us to predict ligament (or ACL) forces directly, this complexity would come at the cost of introducing additional uncertainties related to in-vivo ligament properties (261). Due to the sensitivity of estimated

ACL forces to these ligament properties (e.g. reference strains and ligament stiffness) (261), we opted to exclude ligaments from the model.

The decision to exclude ligaments from the model meant that translations and non-sagittal rotations at the knee needed to be constrained as a function of the knee flexion angle (157), similar to prior studies (101), in order to ensure our predicted muscle forces were as accurate as possible. Another advantage of adopting such constraints is minimising the impact of soft tissue artefact. Prior research has shown that non-sagittal plane knee rotations are particularly sensitive to soft tissue artefact when using skin-mounted marker systems (153). Whilst soft tissue artefact can influence all joint angles, we used a global optimisation inverse kinematics algorithm to obtain our joint angle data, which has previously been shown to be capable of minimising the influence of soft tissue artefact (161). We note that our kinematic data are consistent with prior literature investigating similar change-of-direction tasks using both skin-mounted (255, 256) and bone-pin marker systems (153).

Muscle forces in the present study were estimated using a static optimisation algorithm, which does have some limitations. Unfortunately, muscle forces cannot be directly validated, as in-vivo muscle forces are not practically feasible to measure (118), thus we have no way of directly validating our model predictions. Static optimisation has been shown to provide accurate predictions of in-vivo joint contact forces (159, 171), which serves as an indirect validation of muscle forces due to the high dependency of joint contact forces on muscle forces (118). Furthermore, our predicted muscle activations showed reasonable agreement with experimentally recorded EMG data across the stance phase (Figure 5-2). It has been suggested that static optimisation may not adequately predict co-contraction of muscles. However, our predicted muscle activations (Figure 5-2) as well as recently published data (170) do display evidence of co-contraction. Nevertheless, we recognise that these co-contraction patterns were not necessarily participant-specific but we do not believe this limitation influenced our conclusions. Further research utilising more participant-specific approaches, such as EMG-driven (114) and EMG-hybrid (176) modelling, may yield further clinical insight.

5.7 Conclusion

In conclusion, this study demonstrated that knee-spanning as well as non-knee-spanning muscles contribute substantially to anteroposterior shear forces as well as frontal and transverse plane joint reaction moments at the tibiofemoral joint. Specifically, the vasti and gastrocnemius muscles were found to be the major contributors to the anterior shear reaction force, whilst the biarticular hamstrings and the soleus were the major contributors to the posterior shear reaction

force. The valgus knee joint reaction moment was primarily produced by both knee-spanning (vasti and biceps femoris long head) and non-knee-spanning (soleus) muscles. This moment was opposed by the non-knee-spanning gluteal muscles, particularly the gluteus medius, gluteus maximus and piriformis. The external rotation knee joint reaction moment throughout the weight acceptance phase of sidestep cutting was primarily generated by the vasti and soleus muscles. Based on our consideration of multiple loading states, we conclude that the hamstrings (biceps femoris long head and medial hamstrings), soleus, and the gluteals (especially gluteus medius) have the greatest potential to offset ACL loading during an unanticipated sidestep cutting task. Optimising the function of these muscles should therefore be of high priority in rehabilitative and preventative programs.

Chapter 6 – Study 3: Muscular contributions to medial and lateral tibiofemoral contact forces during sidestep cutting

Publication statement:

This chapter is comprised of the following paper to be submitted to *Osteoarthritis and Cartilage*:

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6.1 Linking paragraph

Chapter 5 investigated the role of individual muscles in the development of surrogate markers of anterior cruciate ligament (ACL) loading: anterior shear force as well as valgus and rotation moments at the knee. This data may allow clinicians to make informed decisions about which muscles to target in order to reduce ACL injury risk. Furthermore, understanding how muscles contribute to knee joint compression is also an important consideration for a number of reasons. Firstly, knee joint compression is thought to play a role in ACL injury, although the exact influence of joint compression on ACL loading is contentious. Some studies have suggested that increased compression may provide increased stability at the knee (24, 81, 262), whilst others have shown increased ACL loading (81, 263-265) or even ACL rupture (79, 80, 266, 267) to occur as a consequence of increased knee joint compression. Due to this contentious relationship, muscle contributions to knee joint compression was not included as an outcome variable in Chapter 5. However, further research could help to elucidate the relationship between knee joint compression and ACL loading, thus knowledge of how muscles contribute to compressive loading may still be useful for clinicians. Additionally, ACL injuries rarely occur in isolation, and concurrent damage to weight-bearing structures such as the menisci and articular cartilage are common (7, 44, 45). Given this, and the association between prior ACL injury and an increased likelihood of knee osteoarthritis (especially in the presence of concurrent meniscal and cartilage damage (254)), understanding the contribution of the hamstrings to tibiofemoral compressive forces, relative to other lower-limb muscles is also warranted. Subsequently, Chapter 6 investigated muscle force contributions to the medial and lateral compartment compressive loading. Such data can further explain the relative contribution of the hamstrings to knee joint loading and could aid in the development of strategies aiming to load or unload specific compartments of the knee. Such information could assist in developing approaches to manage pain and/or degeneration of cartilaginous structures and subchondral bone in the knee. Additionally, knowledge of how muscles contribute to knee joint compression could directly inform neuromuscular retraining strategies aiming to reduce risk of ACL injury.

6.2 Abstract

Compressive loads at the knee during gait has been the subject of many investigations, due to its relationship to pain, debilitation and pathology. However, healthy individuals engage in more vigorous activates, and recent studies have estimated peak compressive loads of around 8 bodyweights during higher impact tasks such as running and sidestep cutting. Compressive loading is known to be primarily modulated by muscle activity. Modulation of compressive forces within the medial and lateral compartments has been considered clinically important for the management of pain and deterioration of knee joint structures. The present study investigated how muscles contributed to the medial and lateral compartment tibiofemoral compressive forces during sidestep cutting. Three-dimensional marker positions, ground reaction forces and electromyographical data was collected from eight healthy males whilst they completed unanticipated sidestep cutting. Musculoskeletal modelling was used to compute the contribution of each lower-limb muscle to compressive loading of each compartment of the knee. The greatest contributors to medial compartment loading was the vasti, gluteus maximus and medius, and the medial gastrocnemius. The greatest contributors to lateral compartment loading was the vasti, adductors, soleus and the gastrocnemius. Medial compartment unloading was primarily accomplished by the soleus, whilst lateral compartment unloading was dominated by the gluteus maximus and medius. This data can be used to inform interventions aiming to modulate compressive loading at the knee. Potential applications include modulating pain following injury, and reducing the progression of cartilage deterioration over time.

6.3 Introduction

Optimal function of the knee joint is fundamental for performance of the most basic activities of everyday living such as standing and locomotion. Due to its location in the lower extremity, the knee experiences substantial loads. For example, in-vivo data have shown that tibiofemoral compressive forces are ~2-3 times bodyweight during walking (268-270) and ~6-7 times bodyweight during jogging (268). In a healthy knee joint, compressive forces are borne by soft tissues such as articular cartilage (271, 272) and menisci (273, 274). However, pathological loading patterns may lead to deterioration of these structures over time, contributing to knee osteoarthritis (275).

Whilst greater tibiofemoral compressive loads have traditionally been attributed as a contributing factor to knee osteoarthritis progression (e.g. obese populations (276)), a growing body of evidence suggests that tibiofemoral loading has a protective effect against cartilage degeneration (150, 277). For example, Andriacchi et al. (275) suggest that repetitive loading during walking is beneficial as it causes conditioning of cartilage. However, healthy individuals engage in a variety of tasks involving weight-bearing of the lower-limb. Many popular sports involve more vigorous tasks such as running, high-impact landing and sudden changes of direction (278, 279). Despite this, investigations of tibiofemoral contact forces during such tasks are limited.

A recent study by Saxby et al. (280) used a musculoskeletal modelling approach to estimate tibiofemoral contact forces during running and sidestep cutting. Results demonstrated contact forces of ~3-8 bodyweights (BW) and ~8 BW during running and sidestep cutting respectively, with muscles identified as the primary stabilisers at the knee. However, Saxby et al. (280) did not establish which specific muscles have the potential to load and unload the medial and lateral compartments of the tibiofemoral joint. Knowledge of how muscles contribute to tibiofemoral compartment loading is important to develop more effective exercise interventions designed to load or unload the knee.

Through “dynamic coupling”, any muscle in the body can induce an acceleration of any segment in the body (38). Prior research (107, 111, 112) has demonstrated the substantial role of non-knee-spanning muscles in the development of compressive tibiofemoral contact forces during walking. However, the way in which a muscle induces accelerations throughout the body is dependent on the orientation of all the segments in the system (38). Due to largely different biomechanical demands between walking and rapid changes of direction, muscular contributions to tibiofemoral compartment loading during high-impact tasks requires further research. Hence, the aim of this study was to investigate muscular contributions to medial and

lateral tibiofemoral compartment compressive loading during a high-impact change-of-direction task. Specifically, we aimed to determine which lower-limb muscles load and unload each compartment of the tibiofemoral joint during an unanticipated sidestep cut, as the function of these muscles could then be targeted in knee cartilage prophylactic measures.

6.4 Methods

6.4.1 Participants

Eight recreationally healthy males (age, 27 ± 3.8 years; height, 1.77 ± 0.09m; mass, 77.6 ± 12.8kg) volunteered to participate in this study. This sample size was based on other musculoskeletal modelling studies that have conducted similar exploratory analysis (e.g. (47, 107)). All participants were healthy and had no current or previous musculoskeletal injury (e.g. ACL injury) likely to influence their ability to perform the required tasks. All participants provided written informed consent and ethical approval was granted by the Australian Catholic University human research ethics committee (approval number: 2015-11H).

6.4.2 Instrumentation

Three-dimensional marker trajectories were collected at 200Hz using a nine camera motion analysis system (VICON, Oxford Metrics Ltd., Oxford, United Kingdom). Ground reaction forces (GRF) were collected via two ground-embedded force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) sampling at 1000Hz. Surface electromyographic (EMG) data were collected at 1000Hz from 10 lower-limb muscles on the dominant leg (defined as the kicking leg; right side for all participants) via two wireless EMG systems (Noraxon, Arizona, USA; Myon, Schwarzenberg, Switzerland).

6.4.3 Procedures

All participants were barefoot during the completion of all tasks. The skin was prepared for surface EMG collection by shaving, abrasion and sterilisation. Circular bipolar pre-gelled Ag/AgCl electrodes (inter-electrode distance of 2cm) were then placed on the vastus lateralis and medialis, rectus femoris, biceps femoris, medial hamstrings, medial and lateral gastrocnemius, soleus, tibialis anterior and peroneus longus muscles in accordance with Surface Electromyography for the Non-Invasive Assessment of Muscle (SENIAM) guidelines (152). EMG-time traces during forceful isometric contractions were visually inspected to verify the correct placement of the electrodes and to inspect for cross-talk. Forty-three 14 mm retroreflective markers were affixed to various anatomical locations on the torso (sternum, the spinous process of the 7th cervical vertebra, the spinous process of a mid-thoracic vertebra, the

tip of each acromion), pelvis (anterior and posterior superior iliac spines), upper-limbs (medial and lateral elbow and distal radius and ulna) and lower-limbs (medial and lateral femoral epicondyles, medial and lateral malleoli, first and fifth metatarsophalangeal joints, calcaneus and three additional markers on each shank and thigh) of each participant.

Each participant completed unanticipated change-of-direction tasks on their dominant leg. Participants were required to perform two single-leg hops for a standardised distance of 1.35m, and then change direction as quickly as possible. Cuts were required to be performed at a 45º angle, upon landing from the second hop. We used a hopping approach based on prior research (153) because it allows approach speed and foot placement on the force plate to be well controlled across participants relative to a running approach. The direction of travel was randomly dictated by a set of timing gates (Smartspeed, Fusion Sport, Australia) that delivered a light signal ~450ms prior to initial contact on the force plates. Floor markings were used to indicate the starting point, the hop landing targets and the required 45º angle from the force plates for the cutting direction. A successful trial required that the participant completed the task correctly with the entire foot landing within the force plate.

6.4.4 Data processing

Marker trajectories were low-pass filtered using a zero-lag, 4^{th} order Butterworth filter with a cut-off frequency of 8Hz. This cut-off frequency was determined via a residual analysis. GRFs were filtered with using the same filter and cut-off frequency as the marker data based on published recommendations (154). EMG data were corrected for offset, high-pass filtered (20Hz), full-wave rectified and low-pass filtered (6Hz) using a zero-lag, 4^{th} order Butterworth filter to obtain a linear envelope. EMG data were normalised to the peak amplitude obtained in each trial.

6.4.5 Musculoskeletal modelling

A 37 degree of freedom (DOF) full-body musculoskeletal model, with 80 musculotendon actuators (lower body) and 17 torque actuators (upper body) (76), was used to perform the musculoskeletal simulations in OpenSim (77). Each hip was modelled as a 3-DOF ball and socket joint. Each knee was modelled as a 1-DOF hinge joint, with other rotational (valgus/varus and internal/external rotation) and translational (anteroposterior and superior-inferior) movements constrained to change as a function of the knee flexion angle (157). A pin joint was used to represent the ankle (talocrural) joint. The head-trunk segment was modelled as a single rigid segment, articulating with the pelvis via a 3-DOF ball and socket joint. Each upper limb was characterised by a 3-DOF ball and socket shoulder joint and single-DOF elbow

and radioulnar joints. The subtalar, metatarsophalangeal, and wrist joints were locked (76). The standard knee joint mechanism was modified to enable the computation of medial and lateral tibiofemoral contact forces via the moment-balancing approach (158). This was done by creating two hinge joints, each with an axis parallel to the anteroposterior axis of the local tibial reference frame. The superior-inferior and anteroposterior location of these contact points were placed at the knee joint centre, whilst the mediolateral location of each point was placed at a generic location in the unscaled model (159), and scaled based on each participant's femoral epicondyle width (160).

The generic model was scaled to each participant's individual anthropometry as determined during a static trial. An inverse kinematics algorithm was used to calculate joint angles by means of a least-squares optimisation that minimised the difference between model and experimental marker positions (161). A residual reduction algorithm (RRA) was then used to make small adjustments to kinematics and torso inertial properties to improve dynamic consistency between kinematic data and measured GRFs. Muscle forces were obtained via static optimisation, which decomposed the RRA-derived joint moments into individual muscle forces by minimising the sum of muscle activations squared, taking into account the physiological force-length-velocity properties (169) of the musculotendinous units. This method of muscle force estimation is computationally efficient and has been used to predict muscle forces in similar high-impact movements (101, 149, 170). The measured GRFs were decomposed into individual muscular contributions by means of a pseudo-inverse-based approach (149, 155, 156). Each muscle's contribution to the medial tibiofemoral contact force was computed by using an adapted version of a previously described method (158). First, each muscle's contribution to the external adduction moment about the lateral contact point was computed by performing inverse dynamics using the RRA-derived joint kinematics and each muscle's contribution to the GRF. Next, the muscle force-derived adduction moment about the lateral contact point was determined by multiplying each muscle force of interest by its respective moment arm about the lateral contact point. In the case of non-knee-spanning muscles, this term was zero due to no moment arm about either contact point in the knee. The difference between the muscle force-derived adduction moment and muscle derived external adduction moment was then divided by the distance between the contact points. This same procedure was used to calculate muscle force contributions to the lateral contact force by performing calculations about the medial contact point.

6.4.6 Outcome variables

Muscular contributions to compressive tibiofemoral compartment loading were quantified by computing the net loading impulse across the stance phase. This was done by integrating the contact force contribution of each muscle with respect to time. Additionally, we observed the time-varying contribution of each major muscle across the stance phase of the change-of-direction tasks.

Muscular contributions were combined according to anatomical and functional groups similar to prior research (107), except where these muscles induced opposing forces/moments of the key tibiofemoral loading parameters. For example, the biceps femoris long head and medial hamstrings (i.e. semimembranosus and semitendinosus) have opposite frontal plane moment arms at the knee, hence the biarticular hamstrings were not grouped together (see Appendix II Table 12 for all functional groupings). Note that we only report on major muscle groups, and did not report any muscle that did not make meaningful contributions to the tibiofemoral compressive forces (see Rajagopal et al. (76) for all musculotendinous actuators included in the model).

6.4.7 Validation and verification

Validation and verification was performed in accordance with current best practice guidelines (113). Qualitative comparisons between model-based predicted activations and experimental EMG data showed good agreement once accounting for appropriate physiological electromechanical delays of ~10-100ms (Figure 6-1). Additionally, the time-varying characteristics of our experimental joint angles and joint moments were within 2SD of published data (153, 255, 256). Comparisons between experimental and simulated variables were evaluated via the normalised root mean square error (nRMSE) and coefficient of determination (R^2). The nRMSE was calculated as:

$$\text{nRMSE}\ (\%) = 100 \times \frac{\sqrt{\frac{\sum_{i=1}^{n} (Experimental_i - Predicted_i)^2}{n}}}{\max(Experimental) - \min(Experimental)}$$

Muscle-derived joint moments (computed from the predicted muscle forces and their respective moments arm) well matched the experimental joint moments (median ± interquartile range, R^2 = 1.0 ± 0.0; nRMSE = 2.0 x 10^{-2} ± 0.03%). Superposition errors between tibiofemoral contact forces derived from the experimental GRFs and GRFs from the foot-ground contact model were also well matched (R^2 = 0.96 ± 0.07; nRMSE = 5.0 ± 2.7%). Residual forces and moments (Appendix II Figure 4) and kinematic tracking errors (Appendix II Table 13) were also acceptable (113).

6.5 Results

The net effect of the majority of muscles was to load both compartments, with the remainder loading one compartment and unloading the other (Figure 6-2). The greatest contributors to the medial compartment compressive impulse were the vasti (673 Ns), gluteus maximus (175 Ns), gluteus medius (143 Ns) and medial gastrocnemius (104 Ns). The greatest contributors to lateral compartment compressive loading were the vasti (745 Ns), the adductors (162 Ns) soleus (143 Ns) and the gastrocnemius (lateral, 119 Ns; medial, 95 Ns). Most of the compressive impulse from the gastrocnemius group was from the second half of stance (Figure 6-3A and C). The other muscles (gluteus medius, gluteus maximus, soleus and vasti), showed more sustained compressive forces across stance, generally peaking around mid-stance (Figure 6-3). All other muscle groups contributed less than 100 Ns to the compressive impulse of either compartment.

Medial compartment decompression impulse was primarily achieved by the soleus (68 Ns), whilst lateral compartment decompression was primarily achieved by the gluteus maximus (48 Ns) and medius (57 Ns). The net impulse of the gluteal and soleus groups was due to relatively sustained decompression forces across the majority of stance (Figure 6-3B and D). The adductors had a net medial compartment impulse of ~0 Ns, but this was from two distinct decompressive force peaks at the first and last ~20% of stance which opposed the predominately compressive influence throughout the mid-portion of stance. All other muscle groups contributed less than 100 Ns to the decompressive impulse of either compartment.

6.6 Discussion

This study demonstrated that both knee-spanning and non-knee-spanning muscles contribute to the tibiofemoral contact forces during a rapid change-of-direction manoeuvre. Most importantly, medial tibiofemoral contact loading was produced by the vasti, gluteus medius, gluteus maximus and the medial gastrocnemius, whilst lateral tibiofemoral loading was produced primarily by the vasti, soleus, and the medial and lateral gastrocnemius. Additionally, we found that most muscles tended to compress both compartments, whilst the remainder tended to load one compartment and decompress the other. To the authors' knowledge, no other studies have calculated muscular contributions to tibiofemoral contact loading during an unanticipated sidestep cut.

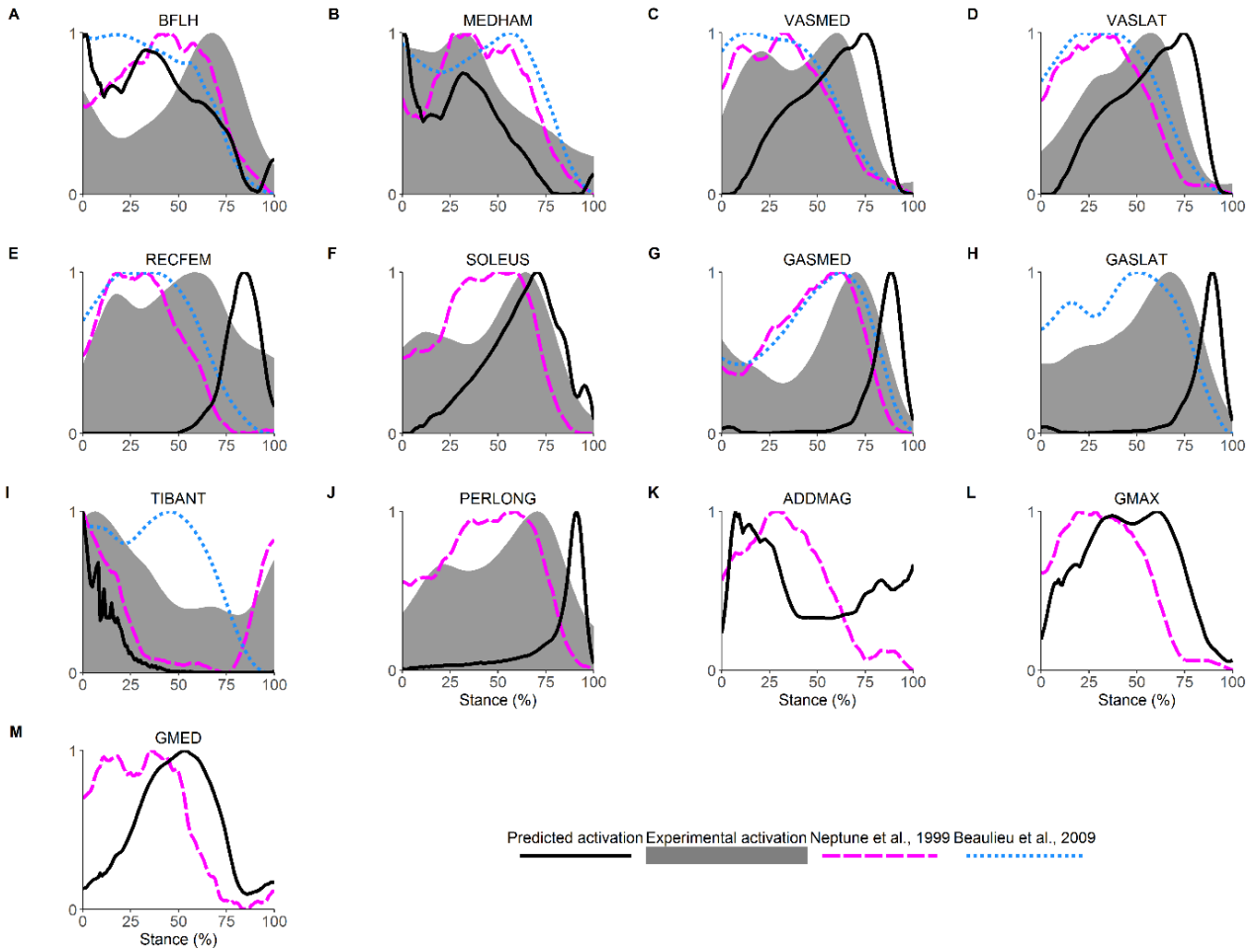

Figure 6-1. Comparison of predicted (black line) and experimental activations (grey shaded) from the current data during the stance phase of the 45º unanticipated sidestep cut. Literature reference activations, magenta dashed line, Neptune et al., *1999; blue dotted line, Beaulieu* et al., *2009. BFLH, biceps femoris long head; MEDHAM, medial hamstrings (semimembranosus and semitendinosus); VASMED, vastus medialis; VASLAT, vastus lateralis; RECFEM, rectus femoris; SOLEUS, soleus; GASMED, gastrocnemius medialis; GASLAT, gastrocnemius lateralis; TIBANT, tibialis anterior; PERLONG, peroneus longus; ADDMAG, adductor magnus; GMAX, gluteus maximus; GMED, gluteus medius.*

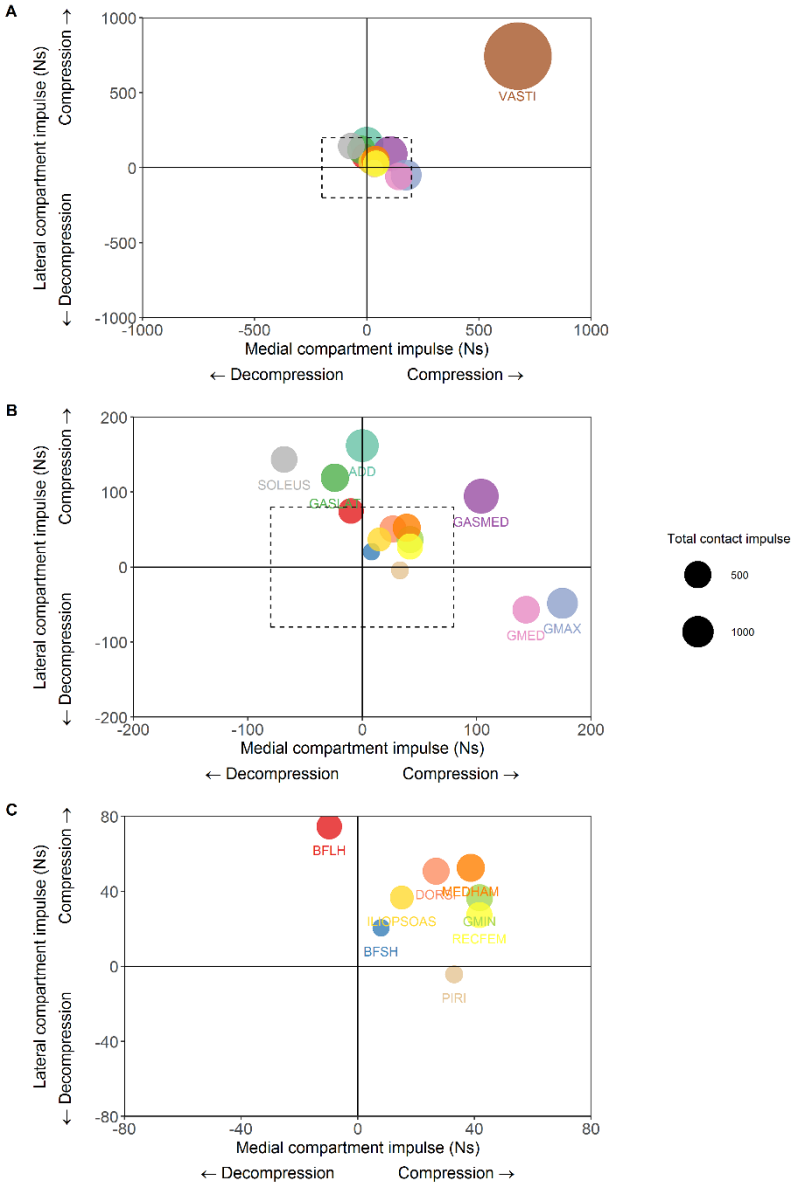

Figure 6-2. Muscular contributions to the net compressive impulse in the medial and lateral tibiofemoral compartments across the stance phase of a 45º unanticipated sidestep cut. Note that the size of each bubble is proportionate to the total tibiofemoral compressive impulse (i.e. impulse of the sum of the medial and lateral compartment compressive load). BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOL, soleus. Panel B is a subset of panel A, and panel C is a subset of panel B (indicated via dashed outline).

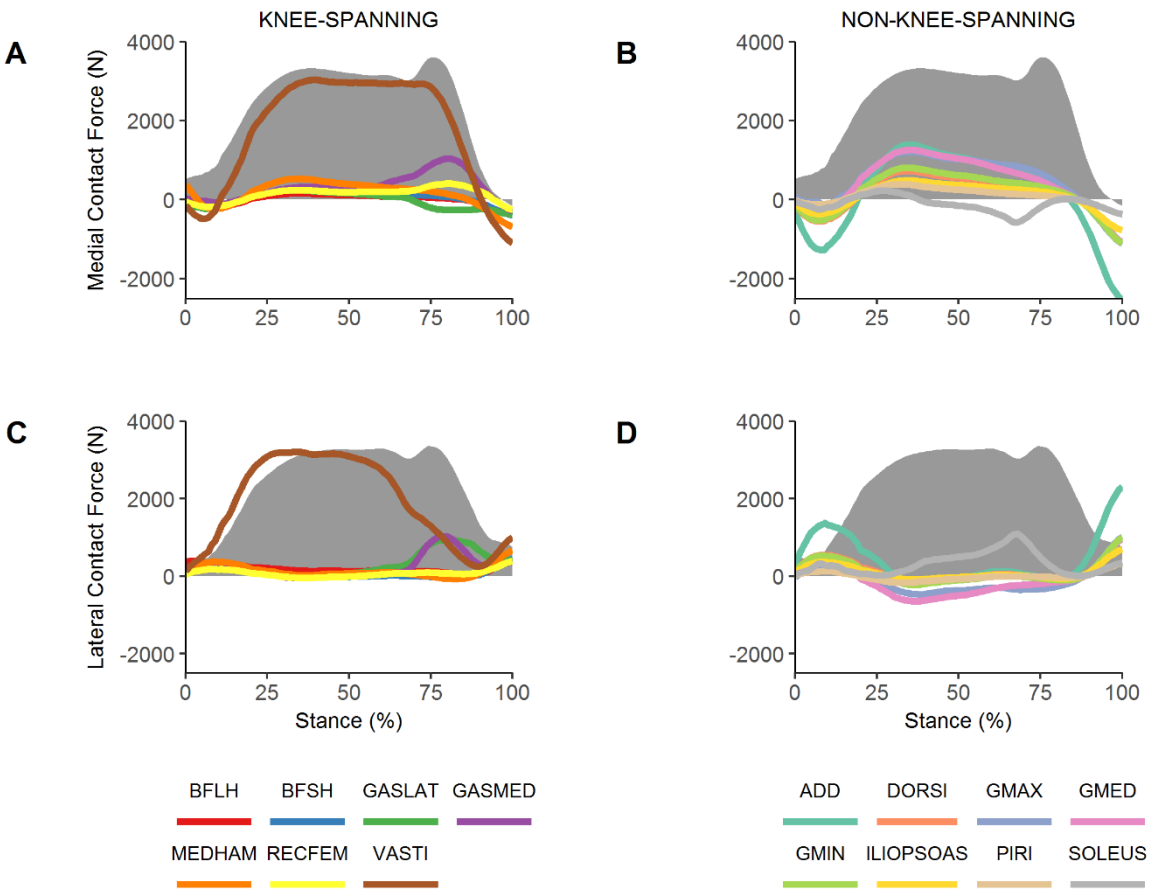

Figure 6-3. Muscular contributions to compressive forces in the medial (top row) and lateral (bottom row) tibiofemoral compartments across the stance phase of a 45º unanticipated sidestep cut. The first column (panels A and C) shows knee-spanning muscles and the second column shows non-knee-spanning muscles. Note that the shaded grey represents the net value from all forces in the system. BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOLEUS, soleus.

The magnitudes of our tibiofemoral contact forces (medial, lateral and total; Figure 6-3) were slightly higher than those previously reported for sidestep cutting (102, 280, 281). For example, medial and lateral compartment peak forces were ~4.7 and 4.4 BW in the current study compared to ~4.1 and 3.8 bodyweights in Saxby et al. (280). These differences may be attributable to different muscle force estimation techniques (EMG-driven vs static optimisation in the current study) and participant populations (mixed genders vs males only in the current study). Additionally, these prior studies used a run and cut task, as opposed to the hop and cut task used in the present study. Arguably, greater hop-related vertical displacement prior to foot contact imposed greater muscular demands to change the vertical momentum. Due to the high dependency of contact forces on muscle forces (118), this would have resulted in greater contact forces. Although this resulted in an increased magnitude of tibiofemoral contact forces, the temporal consistency between our data and that of previous studies (i.e., joint angles, joint moments and EMG (46, 147, 153, 255, 256)) provides confidence that our primary outcome variable (i.e. role of each muscle in the development of tibiofemoral contact forces) was not substantially influenced by the differences in task demands.

Individual muscular contributions to tibiofemoral contact loads have been reported during sidestep cutting (281), running (281) and walking (107, 111, 112, 158, 281). Comparisons with these studies are limited for several reasons. Firstly, Konrath et al. (281), the only study to investigate individual muscle contributions to tibiofemoral contact loads in sidestep cutting and running, consisted of only anterior cruciate ligament (ACL) reconstructed participants. Secondly, this aforementioned study and Winby et al. (158) who investigated walking, did not calculate muscle contributions to the GRF. As such, these studies could not account for dynamic coupling (38) and therefore only investigated the contributions of muscles that crossed the knee. The only studies to consider dynamic coupling and non-knee-spanning muscles investigated walking (107, 111, 112), which has vastly different biomechanical demands to sidestep cutting. Additionally, these studies grouped some muscles differently to the present study (e.g. gastrocnemius, hamstrings); thus, direct comparisons for individual muscles were not always possible. Nevertheless, some consistent functional roles were observed. For example, Konrath et al. (281) found that the vasti and gastrocnemius were the primary contributors to medial compartment compressive loads during a sidestep cut – a finding consistent with that of the present study (Figure 6-1). During walking, Sritharan et al. (107) found that the gluteus maximus and medius were primary contributors to medial compartment compression and lateral compartment decompression, similar to our observations (Figures 6-2B and 6-3B and D). Moreover, they also found that the soleus compressed and

decompressed the lateral and medial compartments, respectively (Figures 6-2B and 6-3B and D). Sritharan et al. (107) also reported that the vasti, gastrocnemius and rectus femoris contributed to compressive loading of both tibiofemoral compartments, whilst two other studies found that these same muscles were primary contributors to total tibiofemoral compressive forces (111, 112), similar to our findings (Figures 6-2 and 6-3A and C).

6.6.1 Practical applications

Our data provides the basis for conservative interventions aiming to influence tibiofemoral joint articular cartilage loading. For example, interventions may be developed to target specific muscles in order to alter the compressive loading of each compartment to prevent further degeneration or pain due to injury or disease. The non-knee-spanning gluteus medius, gluteus maximus and soleus muscles could be targeted for selective unloading of the lateral and medial tibiofemoral compartments, respectively. Such strategies may be useful in allowing the performance of high-impact manoeuvres without provoking pain after injury, potentially facilitating earlier return to sport or weight-bearing activity. However, lower tibiofemoral compressive loading is associated with greater cartilage degeneration following ACL-reconstruction (150). In this respect, our data could be used to determine strategies to increase contact forces in specific compartments. However, further research is needed to determine what strategies are needed for specific injuries and pathologies, as the relationship between compressive loading and pathology is limited. Additionally, the exact nature of any interventions aiming to alter the function of specific muscles requires further research. For example, the function of the soleus would be practically difficult to isolate from the gastrocnemius, a muscle that was found to have a differing contribution to tibiofemoral compressive loading.

6.6.2 Limitations

This study has several limitations. Firstly, a relatively small sample of eight healthy males was included. In addition to including more participants, further research should include different populations such as females, specific athletic subgroups, and pathological populations (e.g. ACL-reconstructed).

Secondly, like a previous study (101) we modelled the knee as a translating hinge joint, whereby translations and non-sagittal rotations at the knee were constrained as a function of the knee flexion angle (157). This was necessary to ensure our predicted muscle forces were as accurate as possible, since the model lacked ligaments. Another advantage of adopting such constraints is minimising the impact of soft tissue artefact given that previous research has

shown that non-sagittal plane knee rotations are particularly affected by soft tissue artefact when using skin-mounted marker systems (153). Whilst soft tissue artefact can influence all joint angles, we used a global optimisation inverse kinematics algorithm to obtain our joint angle data, which has been shown to be capable of minimising the influence of soft tissue artefact (161). We note that our kinematic data are consistent with prior literature investigating similar change-of-direction tasks using both skin-mounted (255, 256) and bone-pin marker systems (153).

Thirdly, muscle forces in the present study were estimated using a static optimisation approach. Muscle forces cannot be directly validated, as in-vivo muscle forces are not practically feasible to measure (118); thus, we have no way of directly validating our model predictions. Static optimisation has been shown to provide accurate predictions of in-vivo joint contact forces (159, 171), which serves as an indirect validation of muscle forces due to the high dependency of contact forces on muscle forces (118). Furthermore, our predicted muscle activations showed reasonable agreement with experimentally recorded EMG data (Figure 6-1). It has been suggested that static optimisation may not adequately predict co-contraction of muscles. Whilst our data showed evidence of co-contraction (Figure 6-1), more participant-specific muscle force predictions, such as EMG-driven (114) and EMG-hybrid (176) modelling, may yield further clinical insight.

Finally, medial and lateral contact points were also not directly measured in-vivo, and were instead scaled based on measured femoral epicondyle width, similar to other studies (158, 280). However, prior studies (107, 158) have perturbed contact point locations by up to 10mm, which resulted in compressive load changes of less than 10%. Therefore, we do not believe that our contact point estimations influenced our findings.

6.7 Conclusions

This study investigated muscular contributions to tibiofemoral contact forces during an unanticipated sidestep cutting task. Both knee-spanning and non-knee-spanning muscles were found to contribute to medial and lateral tibiofemoral compartment loading. Specifically, the medial compartment compressive loading was primarily contributed to by the vasti, gluteus medius, gluteus maximus, and the medial gastrocnemius. The lateral compartment compressive loading was primarily produced by the vasti, soleus, and the medial and lateral gastrocnemius. Most muscles tended to compress both compartments, whilst the remainder tended to compress one compartment and decompress the other. Findings could be used to inform strategies aiming to increase or decrease compressive loading at the knee during high-impact manoeuvres.

Chapter 7 – Study 4: Muscle function during sidestep cutting

Publication statement:

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7.1. Linking paragraph

Chapters 5 and 6 demonstrated the key muscles that can oppose or contribute to the surrogate markers of anterior cruciate ligament (ACL) loading during a sidestep cut, and compressive loading of the tibiofemoral compartments. This data can be used to inform interventions aiming to change the strength or activation of key muscles in order to reduce injury risk, limit degeneration or modulate pain following injury. However, changing the activation of certain muscles may not be favourable, due to deleterious effects on performance. A better understanding of muscle function during a sidestep cut may allow more informed interventions that may strike the optimal balance between minimising injury risk and maximising performance. Subsequently, Chapter 7 investigates the muscular coordination of an unanticipated sidestep cut. Muscle forces and powers were computed, whilst muscle function was defined via contributions to tasks requirements (bodyweight support, propulsion, and redirection) of a sidestep cut.

7.2 Abstract

To investigate lower-limb muscle function during sidestep cutting, prior studies have analysed electromyography (EMG) data together with three-dimensional motion analysis. Such an approach does not directly quantify the biomechanical role of individual lower-limb muscles during a sidestep cut. This study recorded three-dimensional motion analysis, ground reaction force (GRF) and EMG data for eight healthy males executing an unanticipated sidestep cut. Using a musculoskeletal modelling approach, muscle function was determined by computing the muscle contributions to the GRFs and lower-limb joint moments. We found that bodyweight support (vertical GRF) was primarily provided by the vasti, gluteus maximus, soleus and gastrocnemius. These same muscles, along with the hamstrings, were also primarily responsible for modulating braking and propulsion (anteroposterior GRF). The vasti, gluteus maximus and gluteus medius were the key muscles for accelerating the centre-of-mass towards the desired cutting direction by generating a medially-directed GRF. Our findings have implications for designing retraining programs to improve sidestep cutting performance.

7.1 Introduction

Sidestep cutting is frequently performed in sports such as football (278), rugby (282), and handball (279). The ability to cut quickly and effectively is critical to overall performance in these sports. Sidestep cutting technique has also been linked with musculoskeletal injury, such as anterior cruciate ligament (ACL) injuries (11, 14, 15). Less attention, however, has been placed on understanding the fundamental roles of individual lower-limb muscles during this type of change-of-direction manoeuvre. Such knowledge could be important for designing retraining programs to improve sidestep cutting technique.

The execution of locomotion tasks requires the coordination of multiple muscles, since no single muscle can perform all biomechanical functions (283). Neptune and colleagues (46) used surface electromyography (EMG) to provide insight into the role of multiple individual lower-limb muscles during sidestep cutting. However, inferring the biomechanical role of each muscle from EMG data alone is difficult, since the way individual muscles contribute to joint and segment accelerations can sometimes be counter intuitive due to "dynamic coupling" (38).

Muscle actuated simulations have been used previously to predict muscle function during a variety of locomotion tasks (148, 149, 257, 284). The contributions of individual lower-limb muscles to ground reaction forces (GRFs) or centre-of-mass accelerations can be used to understand how muscles achieve key biomechanical functions, such as bodyweight support and forward progression. Such analyses have mostly been limited to walking (48-50, 52, 257, 284) and running (148, 149) in a straight direction. It is possible that lower-limb muscle function during sidestep cutting is distinct from that during walking and running, given the greater demands on accelerating the body's centre-of-mass in a medial direction. Subsequently, the aim of this study was to investigate lower-limb muscle function during a rapid sidestep cut. Specifically, we used a computational musculoskeletal modelling approach involving a GRF decomposition analysis (149, 155, 156) to determine muscular contributions to bodyweight support, forward progression and acceleration of the centre-of-mass in the desired direction of travel during an unanticipated sidestep cut.

7.2 Methods

7.2.1 Participants

Eight recreationally healthy males (age, 27 ± 3.8 years; height, 1.77 ± 0.09m; mass, 77.6 ± 12.8kg) volunteered to participate in this study. All participants had no current or previous musculoskeletal injury likely to influence their ability to perform the required tasks. All participants provided written informed consent to participate in the study. Ethical approval was

granted by the Australian Catholic University Human Research Ethics Committee (approval number: 2015-11H).

7.2.2 Instrumentation

Three-dimensional marker trajectories were recorded at 200Hz using a nine camera motion analysis system (VICON, Oxford Metrics Ltd., Oxford, United Kingdom). GRFs were recorded via two ground-embedded force plates (Advanced Mechanical Technology Inc., Watertown, MA, USA) sampling at 1000Hz. Surface EMG signals were recorded at 1000Hz from 10 lower-limb muscles on the dominant leg (defined as the kicking leg; right side for all participants) via two EMG systems (Noraxon, Arizona, USA; Myon, Schwarzenberg, Switzerland).

7.2.3 Procedures

All participants completed the tasks while barefoot to allow exposure of the foot for marker placement and to avoid any variability in the foot-ground interface. The skin was prepared for recording surface EMG signals by shaving, abrasion and sterilisation. Circular bipolar pre-gelled Ag/AgCl electrodes (inter-electrode distance of 2cm) were then placed on the vastus lateralis and medialis, rectus femoris, biceps femoris, medial hamstrings, medial and lateral gastrocnemius, soleus, tibialis anterior and peroneus longus muscles in accordance with Surface Electromyography for the Non-Invasive Assessment of Muscle (SENIAM) guidelines (152). EMG-time traces during forceful isometric contractions were visually inspected to verify the correct placement of the electrodes and to inspect for cross-talk. Forty-three 14 mm retroreflective markers were affixed to each participant on various anatomical locations, including the torso (sternum, spinous process of the 7^{th} cervical vertebra, spinous process of a mid-thoracic vertebra, tip of each acromion), pelvis (anterior and posterior superior iliac spines), both upper-limbs (medial and lateral elbow and distal radius and ulna) and both lower-limbs (medial and lateral femoral epicondyles, medial and lateral malleoli, first and fifth metatarsophalangeal joints, calcaneus and three additional markers on each shank and thigh).

Each participant completed unanticipated change-of-direction tasks on their dominant (right) leg. Participants were required to perform two single-leg hops for a standardised distance of 1.35m, and then as quickly as possible cut to the left (45^{o} sidestep cut) or to the right (45^{o} crossover cut) upon landing from the second hop. We used a hopping approach based on prior research (153) because it allows speed and foot placement on the force plate to be well controlled across participants relative to a running approach. The direction of travel was randomly dictated by a set of timing gates (Smartspeed, Fusion Sport, Australia) that delivered

a light signal ~450ms prior to initial contact on the force plates. Floor markings were used to indicate the starting point, the hop landing targets and the required 45º angle from the force plates for the cutting direction. A successful trial required that the participant completed the task correctly with the entire foot landing within the force plate. Note that the 45º sidestep cut was the task of interest for this investigation, whereas the crossover cut was only included to ensure cutting direction was unanticipated.

7.2.4 Data processing

Marker trajectories were low-pass filtered using a zero-lag, 4th order Butterworth filter with a cut-off frequency of 8Hz. This cut-off frequency was determined via a residual analysis. GRFs were filtered using the same filter and cut-off frequency as the marker data based on published recommendations (154). EMG data were corrected for offset, high-pass filtered (20Hz), full-wave rectified and low-pass filtered (6Hz) using a zero-lag, 4th order Butterworth filter to obtain a linear envelope. EMG data were normalised to the peak amplitude obtained in each trial.

7.2.5 Musculoskeletal modelling

A 37 degree of freedom (DOF) full-body musculoskeletal model, with 80 musculotendon actuators (lower body) and 17 torque actuators (upper body) (76), was used to perform the musculoskeletal simulations in OpenSim (77). Each hip was modelled as a 3-DOF ball and socket joint. Each knee was modelled as a 1-DOF hinge joint, with other rotational (valgus/varus and internal/external rotation) and translational (anteroposterior and superior-inferior) movements constrained to change as a function of the knee flexion angle (157). A pin joint was used to represent the ankle (talocrural) joint. The head-trunk segment was modelled as a single rigid segment, articulating with the pelvis via a 3-DOF ball and socket back joint. Each upper limb was characterised by a 3-DOF ball and socket shoulder joint and single-DOF elbow and radioulnar joints. The subtalar, metatarsophalangeal, and wrist joints were locked (76). The generic model was scaled to each participant's individual anthropometry as determined during a static trial. An inverse kinematics algorithm was used to calculate joint angles by means of a least-squares optimisation that minimised the difference between model and experimental marker positions (161). A residual reduction algorithm (RRA) was then used to make small adjustments to kinematics and torso inertial properties to improve dynamic consistency between kinematic data and measured GRFs. Muscle forces were obtained via static optimisation, which decomposed the RRA-derived joint moments into individual muscle forces by minimising the sum of muscle activations squared, taking into account the physiological force-length-velocity properties (169) of the musculotendinous units. This

method of muscle force estimation is computationally efficient and has been used to predict muscle forces in similar high-impact movements (101, 149, 170). We then performed a GRF decomposition analysis (149, 155, 156) to determine muscular contributions to the GRFs.

7.2.6 Outcome variables

Muscular contributions to "support" as well as "braking and propulsion" are typically defined by their contributions to the vertical and anteroposterior GRFs, respectively. However, these definitions have been applied for planar tasks such as walking and running (148, 149, 257, 284). Change-of-direction manoeuvres require appreciable acceleration of the body's centre-of-mass out of the sagittal plane, thus muscular contributions to the mediolateral GRF were also considered. Finally, consistent with other studies investigating muscle function (e.g. (52, 149)), we calculated muscular contributions to lower-limb joint moments.

Certain muscles were combined into functional groups consistent with prior research (107). Note that we only report on major muscle groups, and did not report on muscles that were not found to make meaningful contributions to the outcome variables (see Rajagopal et al. (76) for all musculotendinous actuators included in the model). Note that swing limb muscles made trivial contributions to the GRF, thus only stance limb muscles are reported.

7.2.7 Validation and verification

Validation and verification of model predictions was performed in accordance with current best practice guidelines (113). Qualitative comparisons between model-based predicted muscle activations and experimental EMG recordings showed good agreement after accounting for appropriate physiological delays of ~10-100ms (Figure 7-1). Additionally, the time-varying characteristics of our RRA-derived joint angles (Appendix II Figure 2) and joint moments (Appendix II Figure 3) were within 2SD of published data (153, 255, 256). Comparisons between experimental and simulated variables were evaluated via the normalised root mean square error (nRMSE) and coefficient of determination (R^2). The nRMSE was calculated as:

$$\text{nRMSE}\ (\%) = 100 \times \frac{\sqrt{\frac{\sum_{i=1}^{n} (Experimental_i - Predicted_i)^2}{n}}}{\max(Experimental) - \min(Experimental)}$$

Muscle-derived joint moments (computed from the predicted muscle forces and their respective moment arms) were well matched with the experimental joint moments (median ± interquartile range, $R^2 = 1.0 \pm 0.0$; nRMSE = $2.0 \times 10^{-2} \pm 0.03\%$). Superposition errors between experimental and simulated GRFs were also well matched ($R^2 = 0.93 \pm 0.06$; nRMSE = $9.8 \pm 3.7\%$). Residual

forces and moments (Appendix II Figure 4) and kinematic tracking errors (Appendix II Table 13) were also acceptable (113).

7.3 Results

7.3.1 Braking and propulsion

Anteroposterior GRFs were characterised by a braking force (posteriorly-directed GRF) in the first half of stance, and propulsion (anteriorly-directed GRF) in the second half (Figure 7-2A). The anteroposterior GRF was primarily modulated by the hip extensors, knee extensors and the ankle plantar-flexors. Specifically, braking throughout stance was primarily generated by the vasti (up to 335N) and soleus (up to 151N) muscle groups. The hip extensors were the primary contributors to propulsion for the first ~60% of stance, with the gluteus maximus and hamstrings producing up to 142N and 102N of the anteriorly-directed GRF, respectively. The contributions of these two muscle groups declined thereafter, with the ankle plantar-flexors taking over as the dominant contributors to propulsion (gastrocnemius, up to 312N; soleus, up to 93N).

7.3.2 Vertical support

Vertical support was primarily generated by the gluteus maximus, vasti, soleus and gastrocnemius (Figure 7-2B). The gluteus maximus was the dominant contributor to vertical support in the first ~10% of stance, and produced up to 356N of vertical GRF at ~25% of stance. This contribution declined thereafter. The vasti and soleus became the primary vertical support muscles from ~10% to ~75% of stance, producing up to 1091N and 704N of vertical force, respectively. The gastrocnemius produced up to 548N at ~80% of stance, and declined thereafter along with the contributions from the vasti and soleus.

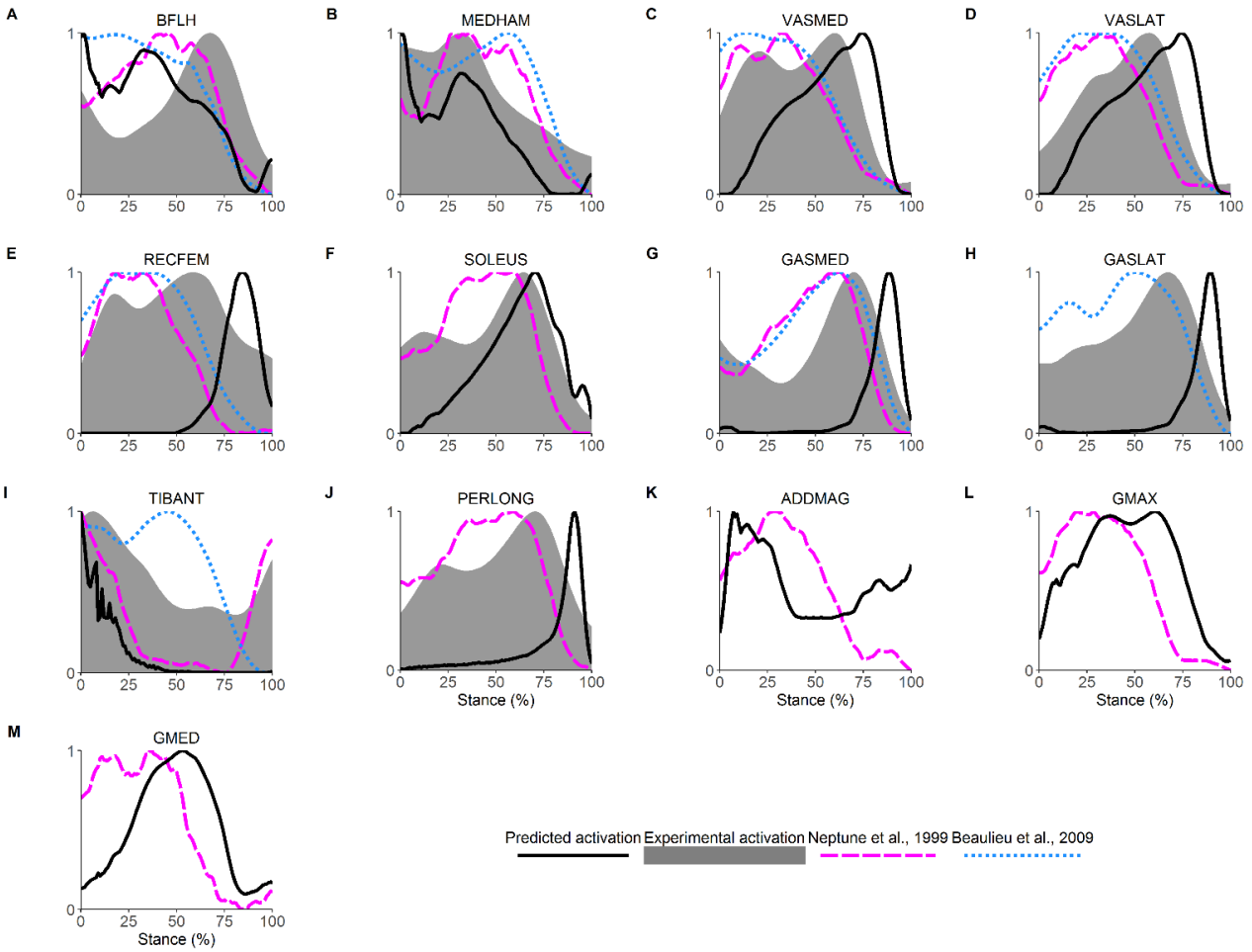

Figure 7-1. Comparison of predicted (black line) and experimental activations (grey shaded) from the current data during the stance phase of the 45º unanticipated sidestep cut. Literature reference activations, magenta dashed line, Neptune et al., 1999; blue dashed line, Beaulieu et al., 2009. BFLH, biceps femoris long head; MEDHAM, medial hamstrings (semimembranosus and semitendinosus); VASMED, vastus medialis; VASLAT, vastus lateralis; RECFEM, rectus femoris; SOLEUS, soleus; GASMED, gastrocnemius medialis; GASLAT, gastrocnemius lateralis; TIBANT, tibialis anterior; PERLONG, peroneus longus; ADDMAG, adductor magnus; GMAX, gluteus maximus; GMED, gluteus medius.

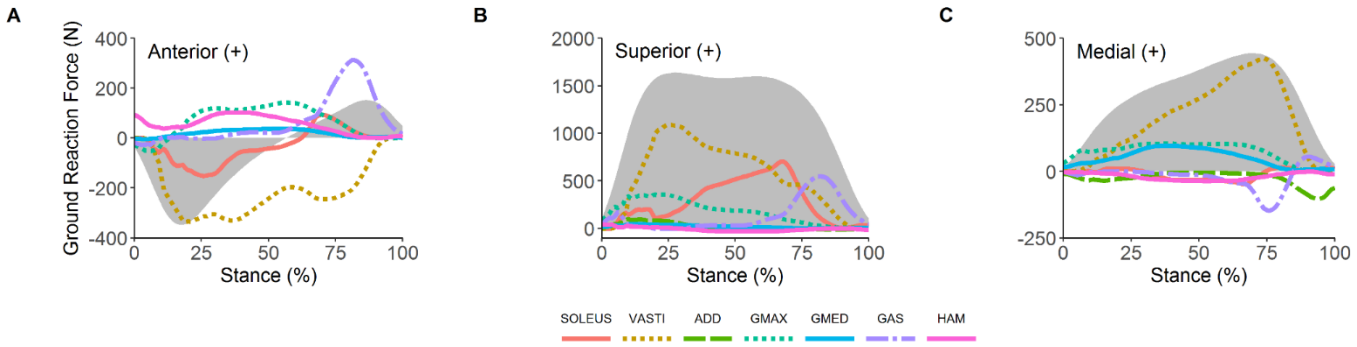

Figure 7-2. Muscular contributions to ground reaction forces during the stance phase of the 45° unanticipated sidestep cut. Panel A, anteroposterior; B, superior-inferior; C, mediolateral. Note that the shaded grey represents the net experimental value. SOLEUS, soleus; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); GMAX, gluteus maximus; GMED, gluteus medius; GAS, gastrocnemius (gastrocnemius medialis and lateralis); HAM, hamstrings (biceps femoris long head, semimembranosus and semitendinosus).

7.3.3 Mediolateral redirection

The net GRF was medially-directed throughout stance, indicating acceleration of the centre-of-mass towards the desired cutting direction (Figure 7-2C). Medial acceleration of the centre-of-mass was generated primarily by the vasti, gluteus maximus, and gluteus medius. The vasti produced up to 424N of the medially-directed GRF, peaking at ~75% of stance. Also, the gluteus maximus and medius respectively produced up to 105N and 96N of the medially-directed GRF. The gastrocnemius and adductors generated a laterally-directed GRF (thereby opposing acceleration of the centre-of-mass in the direction of travel), with these muscles producing up to 147N and 102N, respectively, during late stance. In the last 15% of stance, both the gastrocnemius and soleus accelerated the centre-of-mass medially, although these contributions were no greater than 55N and 15N, respectively.

7.3.4 Muscle contributions to lower-limb joint moments

Overall, the major contributors to the GRFs were also the major contributors to the net joint moments (Figure 7-3). Muscles that contributed to propulsion tended to contribute to the hip extension, knee flexion or ankle plantar-flexion moments. The exception was soleus, which was the dominant contributor to the ankle plantar-flexion moment during the first half of stance (Figure 7-3E), but it contributed to braking (posteriorly-directed GRF) during this period (Figure 7-2A). The muscles that were responsible for vertical support tended to be the major contributors to the hip extension, knee extension, or ankle plantar-flexion moments. The biarticular hamstrings, however, provided an appreciable contribution to the hip extension moment (Figure 7-3A), but were responsible more so for generating propulsion rather than vertical support (Figure 7-2B). The gluteus medius and maximus were the dominant contributors to the hip abductor moment, whereas the hip adductors contributed to the hip adductor moment at the start and end of stance (Figure 7-3B).

7.4 Discussion

The purpose of this study was to evaluate lower-limb muscle function during an unanticipated sidestep cut. Our main findings were as follows: firstly, braking and propulsion as well as vertical support during a sidestep cut were primarily modulated by the vasti, gluteus maximus, soleus, and gastrocnemius muscles; and secondly, by contributing to the medial GRF, the vasti, gluteus maximus and gluteus medius were the most important muscles for accelerating the centre-of-mass towards the desired cutting direction.

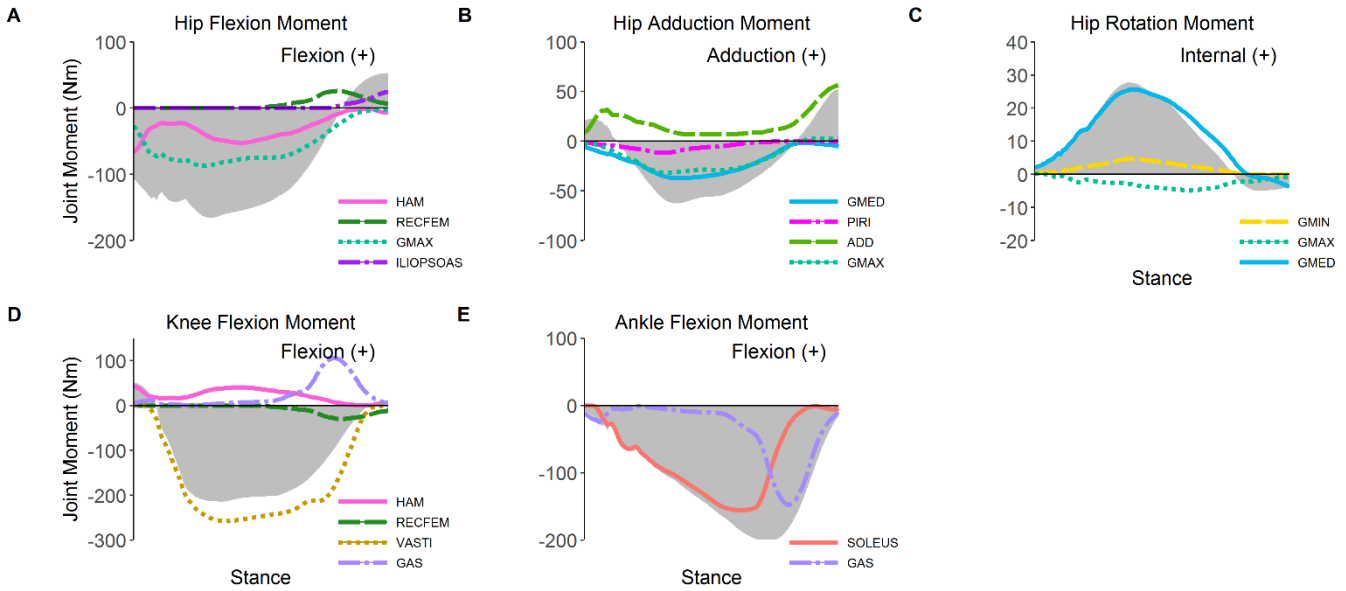

Figure 7-3. Muscular contributions to the lower-limb net joint moments during the stance phase of a 45° unanticipated sidestep cut. Note that the shaded grey represents the net experimental value. HAM, hamstrings (biceps femoris long head, semimembranosus and semitendinosus); RECFEM, rectus femoris, GMAX, gluteus maximus; ILIOPSOAS, iliopsoas (iliacus and psoas major); GMED, gluteus medius; PIRI, piriformis; ADD, adductors (adductor brevis, longus and magnus); GMIN, gluteus minimus; VASTI, vasti (vastus intermedius, lateralis and medialis); GAS, gastrocnemius (gastrocnemius medialis and lateralis); SOLEUS, soleus.

7.4.1 Vertical support

To our knowledge, no previous studies have used computational musculoskeletal modelling to quantify the contributions of individual lower-limb muscles to the GRFs during sidestep cutting. We have therefore compared our data with prior studies investigating walking (47-52) and running (148, 149) in a straight line as well as turning gait (53, 54). For example, these studies have consistently found that vertical support is generated by the vasti and gluteus maximus during early stance, after which the gastrocnemius and soleus became the dominant contributors to vertical support. Our observations were similar (Figure 7-2B), although we found that the relative contributions of these muscle groups were different during sidestep cutting. Specifically, we found that the vasti made relatively larger contributions to vertical support than the ankle plantar-flexors, whereas the opposite has typically been reported for walking (47-50) and running (148, 149). These observed differences could reflect the specificity of muscle function during sidestep cutting. For example, the sidestep cut requires a larger medially-directed GRF compared to walking (51) and running (177). Since soleus generated a laterally-directed GRF for the majority of stance (Figure 7-2C), there may have been an overall shift in strategy towards greater reliance on the vasti, which produced a medially-directed GRF (Figure 7-2C). This explanation is supported by the similar peak soleus muscles forces but substantially higher peak vasti muscle forces in the present study (Appendix II Figure 5) when compared to running (149). Nevertheless, we acknowledge that these differences could also be attributable to specific modelling techniques. For example, Dorn and colleagues (155) found that certain foot-ground contact models predict greater contributions to vertical support from the vasti compared to the soleus during running, whilst other foot-ground contact models predict the opposite.

7.4.2 Mediolateral redirection

We found that the vasti, gluteus maximus and gluteus medius were the dominant contributors to redirecting the centre-of-mass acceleration towards the direction of travel in the frontal plane via their contribution to the medially-directed GRF (Figure 7-2C). In contrast, the ankle plantar-flexors and the adductors were primarily responsible for accelerating the centre-of-mass in the opposite direction (Figure 7-2C). Whilst these functional roles are mostly similar to previous investigations of walking (50-52), our observation that the vasti contributes to a medially-directed GRF is in contrast to prior literature for walking (50-52) and turning gait (54). The way in which a muscle force results in segment accelerations is dependent on the configuration of the various joints in the system (38). Hence, the differing segmental

orientations (i.e. whole body kinematics) between sidestep cutting compared to walking and running (164, 284) may explain the differing roles between these locomotor tasks. For example, the stance leg was abducted during sidestep cutting (Appendix II Figure 2), whereas the stance leg is adducted during walking (284). These contrasting limb orientations could redirect the net contribution from the vasti to involve acceleration of the centre-of-mass vertically and medially during sidestep cutting compared to vertically and laterally during walking (50-52).

7.4.3 Braking and propulsion

We found that braking (posteriorly-directed GRF) was primarily generated by the vasti throughout stance and by the soleus during the first ~60% of stance, whereas propulsion (anteriorly-directed GRF) was primarily generated by the gluteus maximus and hamstrings during the first 60-70% of stance, and the gastrocnemius and soleus during late stance. Whilst these findings are generally consistent with that for other forms of locomotion (47, 48, 50, 148, 284), previous studies have typically found that the gluteus maximus primarily accelerates the centre-of-mass posteriorly. As previously discussed, this contrasting result is probably attributable to differing segmental orientations (38) in sidestep cutting compared to walking and running (148, 284).

7.4.4 Sidestep cutting performance

Determining the specific role of each muscle in the coordination of a rapid sidestep cut may have implications for sidestep cutting performance. For example, prior studies have shown that a greater peak ankle plantar-flexor moment (285, 286) and peak ankle power generation (286) are associated with faster sidestep cutting times. Our data concur with these results, as we found that the main ankle plantar-flexors (gastrocnemius and soleus) played a critical role in vertical support, and were the dominant generators of propulsion during late stance (Figure 7-2A). Additionally, these muscles were also found to have a role in accelerating the centre-of-mass towards the desired cutting direction, via their contributions to a medially-directed GRF during the final 15% of stance (Figure 7-2C). Havens and colleagues (285) also found that greater sagittal hip power generation was associated with faster sidestep cuts. Our data also support the importance of the hip extensors (gluteus maximus and hamstrings), as these muscles were main generators of propulsion during the first 60% of stance. Additionally, the gluteus maximus was also found to contribute to vertical support as well as acceleration of the centre-of-mass towards the desired cutting direction, demonstrating the importance of this muscle for sidestep cutting performance.

7.4.5 Implications

Our data may also help inform neuromuscular training interventions, which aim to minimise injury risk and maximise performance. For example, rapid change-of-direction tasks are a common mechanism of ACL injury (11, 14, 15) and previous studies have shown that quadriceps and hamstring muscle forces tend to load and unload the ACL, respectively. Our data show that the vasti play a fundamental role in supporting bodyweight and accelerating the centre-of-mass towards the desired cutting direction. This finding suggests that maximising quadriceps force production may be critical for optimal performance, but it could also expose the ACL to greater load. In addition to their role in protecting the ACL from these quadriceps forces (27), our data suggest that the hamstrings contribute to propulsion (anteriorly-directed GRF) during the first two thirds of stance. It is therefore possible that facilitating hamstrings function during sidestep cutting has the benefit of minimising injury risk without impairing performance. Further research, however, is needed to verify this assertion.

7.4.6 Limitations

The present study involved a cohort of eight healthy recreationally-active males. Further research should consider the influence of different populations such as females, specific athletic subgroups, and people with pathology. Additionally, only 45º sidestep cutting was investigated. It is possible that greater or smaller cutting angles would alter muscle coordination strategies, which therefore warrants further study.

Muscle forces in the present study were estimated using a static optimisation approach, which does have some limitations. Unfortunately, muscle forces cannot be directly validated because in-vivo muscle forces are not practically feasible to measure (118), thus we have no way of directly validating our model predictions. Static optimisation has been shown to be capable of providing accurate predictions of in-vivo joint contact forces at least for walking (159, 171), which serves as an indirect validation due to the high dependency of joint contact forces on muscle forces (118). Furthermore, our predicted muscle activations showed reasonable agreement with experimentally recorded EMG data across the stance phase (Figure 7-1). It has been suggested that static optimisation may not adequately predict co-contraction of muscles. However, our predicted muscle activations, as well as recently published data (170), provide evidence of co-contraction. Nevertheless, we recognise that these co-contraction patterns were not necessarily participant-specific, but we do not believe this limitation influenced our conclusions. Further research utilising alternative modelling approaches, such as EMG-driven (114) and EMG-hybrid (176) models, may yield further insight.

We also acknowledge that the GRF decomposition technique relies on a foot-ground contact model that is susceptible to modelling errors (156) and can influence the interpretation of muscle function (155). However, the foot-ground contact model implemented in the present study allowed for a foot-phase-specific constraint set that is more likely to be robust against various foot-strike patterns (156). Additionally, verification of our outcomes via the principle of superposition indicated that our model adequately reproduced experimentally measured GRFs, providing further confidence in the suitability of the foot-ground contact model.

7.5 Conclusion

In summary, this study investigated lower-limb muscle function during a rapid sidestep cut. We found that the vasti, gluteus maximus, soleus, gastrocnemius and hamstrings were important for modulating anteroposterior progression during the stance phase of an unanticipated sidestep cut. These same muscles (except the hamstrings) were also important for supporting bodyweight, while the vasti, gluteus maximus and the gluteus medius played a critical role in accelerating the centre-of-mass towards the desired cutting direction. These functional roles should be considered in neuromuscular retraining programs which aim to reduce injury risk and/or maximise performance.

Chapter 8 – General discussion and conclusion

This program of research investigated the role of muscle force in the development of knee joint loading. Initially, the thesis began investigating the potential relationship between prior hamstring strain injury (HSI) and anterior cruciate ligament (ACL) injury. The initial literature review (Chapter 2) confirmed that muscle force from the hamstrings have extensive and consistent evidence demonstrating their ability to unload the ACL.

Chapter 4 was a systematic review and meta-analysis that revealed that whilst hamstring isometric strength and flexibility deficits resolve rapidly following HSI, deficits in hamstring concentric and eccentric strength appear to persist beyond return to play. Additionally, concentric and eccentric hamstring to concentric quadriceps strength ratios were also persistently reduced following return to play from HSI. Due to the importance of hamstring muscle force for unloading the ACL, this data supported the potential relationship between prior HSI and ACL injury. It was also apparent that post-HSI assessments rarely considered the function of other lower-limb muscles, nor was there examination of function during multi-planar movements. As a result, further work studying lower-limb muscle function during potentially ACL injurious manoeuvres was warranted to better understand the contribution of the hamstrings to knee joint loading compared to other lower-limb muscles. Subsequently, a series of musculoskeletal modelling studies were undertaken to investigate lower-limb muscle function during unanticipated sidestep cutting.

Chapter 5 investigated how lower-limb muscle force contributed to the key surrogate markers of ACL load: anterior shear force, the knee valgus moment and the knee internal rotation moment. It was found that the hamstrings were indeed a critical muscle group, as they strongly opposed the anterior shear force and limited frontal and transverse plane loading across the weight acceptance phase. Additionally, it was found that non-knee-spanning muscles were also important. The soleus was found to oppose anterior shear forces, whilst the gluteus medius, gluteus maximus and the piriformis all strongly opposed the knee valgus moment. This data may have implications for injury prevention programs, which often aim the change the strength or activation of key muscle groups to reduce injury risk.

Chapter 6 investigated how lower-limb muscles contributed to the compressive loading of the knee, due to the potential role of knee joint compression in ACL injury and concurrent damage to surrounding weight-bearing structures. It was identified that compressive loading was primarily produced by the vasti and gastrocnemius. The gluteal maximus and medius were dominant producers of medial compartment compression, and lateral compartment

decompression. The opposite influence was noted for the soleus. The hamstring muscles contributed compressive force, but this was less substantial than the aforementioned muscles.

Chapter 7 further elucidated muscle function in relation to the coordination of a sidestep cut. The hamstrings were found to play an important role in the performance of a sidestep cut, but this was secondary to the vasti, gluteus maximus, gastrocnemius and soleus. All four of these muscles were major contributors to bodyweight support and modulating anteroposterior progression, whilst the vasti and gluteus maximus (along with the gluteus medius) were primarily responsible for redirecting the centre-of-mass toward the direction of travel. These findings have implications for neuromuscular retraining programs, which may aim to increase performance or minimise injury risk.

8.1 Significance of research

Prior to the present work, no previous studies had investigated the link between prior HSI and future ACL injury. Due to the relatively low incidence of ACL injuries, establishing this link would require a large prospective study that was beyond the scope of this thesis. However, the studies conducted provide the foundation for establishing this relationship, whilst revealing numerous other novel insights which may aid in the development of preventative and rehabilitative strategies for ACL injury.

Chapter 4 showed that whilst isometric strength deficits in the hamstrings tend to resolve during rehabilitation, concentric and eccentric strength deficits persist well beyond return to play. This finding has significant clinical implications, as lower eccentric hamstring strength is associated with increased risk of HSI (249, 287, 288). Since the publication of the study described in Chapter 4, researchers have proposed that the resolution of isometric but not eccentric strength may be due to current rehabilitation progression guidelines, which may unnecessarily delay the implementation of eccentric loading (289). These findings observed in Chapter 4 have therefore aided in identifying the specific areas that current rehabilitation strategies do not effectively target and encouraging the development of alternative rehabilitation approaches which may be more effective at improving rehabilitation outcomes.

Chapters 5, 6 and 7 used musculoskeletal modelling to investigate muscle function during a common ACL injury mechanism, sidestep cutting. Whilst musculoskeletal modelling is not without limitations (discussed below), it also offers several substantial benefits which directly relate to the impact and innovation of the work described in Chapters 5, 6 and 7. Firstly, musculoskeletal modelling allows for the estimation of numerous physiologically relevant parameters which are otherwise extremely difficult or impossible to measure. For example,

muscle forces during complex movements cannot be measured in-vivo non-invasively with current technology. The modelling pipeline used in Chapters 5, 6 and 7 allowed the estimation of muscle forces during a sidestep cut, which therefore allowed for the assessment of muscle function during a commonly reported ACL injury mechanism. Additionally, musculoskeletal modelling allows relationships in a cause-effect manner. For example, it has been proposed that gluteus medius strength is important to limit valgus loading of the knee (132, 290). Chapter 5 provided the biomechanical basis for this assertion, by showing that muscle force from the gluteus medius induces a varus reaction moment (thus opposing knee valgus loading) via its contributions to the ground reaction force (GRF) during the weight acceptance phase of an unanticipated sidestep cut. This data suggests that it may behove practitioners to target, for example, the gluteus medius in strengthening or neuromuscular retraining programs aiming to reduce ACL injury risk.

Chapters 6 and 7 also provide important considerations for the development of neuromuscular retraining programs. For example, although Chapter 5 demonstrated the vasti induced an anterior shear force and valgus reaction moment during a sidestep cut, they also play a critical role in supporting bodyweight and accelerating the centre-of-mass toward the direction of intended travel (Chapter 7). Subsequently, strategies that aim to reduce vasti force in order to reduce ACL injury risk may also compromise performance. Additionally, the vasti contribute heavily to compressive forces at the tibiofemoral joint (Chapter 6), thus reducing vasti force may also accelerate the deterioration of articular cartilage following ACL injury (150). Instead, the data reported in this thesis suggests that practitioners should aim to increase the contribution of ACL agonists identified in Chapter 5, such as the hamstrings, soleus and gluteus medius. Not only do these muscle groups have the potential to reduce ACL loading during sidestep cutting, but also tend to have opposing biomechanical roles in relation to tibiofemoral compressive loading (Chapter 6) and the coordination of a sidestep cut (Chapter 7). Targeting these muscles may therefore facilitate a reduction in ACL injury risk whilst limiting unwanted consequences.

8.2 Methodological discussion

This program of research involved the use of computational modelling in order to investigate complex biomechanical concepts. Since the methodological rigour of this approach has an impact on the real-world applications, a technical discussion of the methods is warranted. Subsequently, the following section covers these methodological aspects in more detail,

including a discussion of limitations and the details of additional post-hoc analysis to determine the sensitivity of the conclusions to key assumptions and uncertainties.

8.2.1 Sample

Due to the extensive computations performed in this work, a sample size of eight was used in Chapters 5, 6 and 7. This is similar to other studies using similar methodology (101, 107, 149). Additionally, statistical techniques that may be biased by small sample sizes were not used. The experimental data compared well with prior investigations of similar movements (e.g. (280)), thus providing confidence that the findings were unlikely to be atypical. Future work should consider larger sample sizes, and other populations such as females and pathological populations (e.g. ACL-reconstructed and hamstring strain injured). It should be noted that the current thesis chose to exclusively study males, as HSI is more common in males compared to females (291). Given one of the intentions of this thesis was to provide a deeper evidence-based foundation to study the link between prior HSI and future ACL injury, the use of male participants was deemed necessary. Whilst the relative rates of ACL injury are higher in females compared to males, the absolute number of ACL injuries is greater in males than in females (55). Regardless, the higher relative incidence of ACL injuries in females compared to males warrant future work in females.

8.2.2 Kinematics

The studies described in Chapters 5, 6 and 7 were also dependent on skin-surface marker derived kinematics, which are prone to errors due to soft tissue artefact, particularly for non-sagittal tibiofemoral rotations (153). However, a global optimisation method was used to compute joint angles, and this method has been shown to be capable of reducing the influence of soft tissue artefact (161). Additionally, non-sagittal knee rotations were constrained to change as a function of knee angle (157). A sensitivity analysis was performed to verify that this assumption did not influence the conclusions of each chapter. For a single participant, frontal and transverse plane alignments were perturbed by 10º in each direction, and then repeated the computations performed in Chapters 5, 6 and 7. The magnitude of the perturbation was selected based on the absolute error introduced by soft tissue artefact during sidestep cutting (153). It was found that 10º perturbations changed the magnitude of the reaction forces and moments, but did not change the general trends with respect to time (Appendix III). Additionally, the primary conclusions of each study (i.e. the role of each muscle) were robust (Appendix III). The only potential exception was the vasti in the second study (Chapter 5), which tended to have larger variability than other muscle groups. Despite this variability, the

qualitative role was generally consistent, with the minor exception of the last 20% of weight acceptance for the anteroposterior shear force. Although the reasons for this variability in the vasti compared to other muscles are unclear, it may be because the vasti is a grouping of three separate muscles, each of which produced substantial amounts of muscle force (Appendix II Figure 5).

8.2.3 Muscle force estimation

The studies described in Chapters 5, 6 and 7 used static optimisation to estimate muscle forces. Whilst muscle forces cannot be directly validated, indirect validation is possible via comparison of the estimated joint contact force with in-vivo measurements from instrumented joint implants (113). Current data suggests that static optimisation is capable of predicting contact forces well (159, 171), supporting the use of this algorithm for the thesis.

Despite this, the static optimisation algorithm implemented in OpenSim (77) does not account for certain muscle-tendon-unit physiological parameters, such as activation dynamics or tendon compliance. This could influence certain aspects of the simulations. For example, the maximum isometric force of each muscle in the generic model had to be increased, similar to other studies that investigated a high-impact task (e.g. (101, 170)). This was needed in the present thesis, as the gastrocnemius muscle group was unable to produce sufficient force with the baseline strength in the generic model for any of the participants' trials. This could be because in reality the gastrocnemius has a relatively high tendon compliance (292), thus the rigid tendon assumption is less valid for this muscle. A rigid tendon assumption could cause the muscle to be unable to produce sufficient force, since a compliant tendon can allow a muscle to function on more favourable portions of the force-length and/or force-velocity spectrum (293, 294). Since the primary outcomes of this thesis were not directly related to the activation of each muscle, the consequences of the rigid tendon assumption did not influence the conclusions made. However, is worth noting that alternative algorithms for muscle force estimation, such as computed muscle control (115), do account for activation dynamics and tendon compliance, potentially resulting in more physiologically reasonable estimations of musculotendon dynamics. However, due to forward integration requirements, muscle force estimations from computed muscle control are very sensitive to mass and inertial parameters of various body segments (173). Since mass and inertial parameters of individual body segments were not directly measured, an approach more robust to mass and inertial uncertainties, such as static optimisation, had greater appeal for the work in this thesis. Recently developed dynamic optimisation approaches (116) can account for activation dynamics and

tendon compliance, whilst being more robust to mass and inertial uncertainties as forward integration is not required. Dynamic optimisation, however, comes at a greater computational cost (116). Additionally, static and dynamic optimisation solutions have been shown to be practically equivalent, at least in walking (117). Future work should explore these newly developed dynamic optimisation approaches to determine their appropriateness for movements such as sidestep cutting.

Static optimisation also does not account for participant-specific muscle activation patterns, and it is unknown if the chosen cost function (minimising the sum of muscle activations squared) is ideal for the task of interest. However, the predicted activations showed reasonable agreement with measured electromyographical (EMG) data (Figures 5-2, 6-1 and 7-1), providing confidence that the simulations from this method were physiologically reasonable. Some discrepancies were evident, however the following points warrant consideration. One important consideration is that static optimisation does not account for electromechanical delay, thus a time-lag is expected between experimental and predicted activations. Due to the large variation in reported electromechanical delays between different muscles (295-297), time-shifting the data to correct for these delays was not attempted. As a consequence, the goodness of fit may appear worse for certain muscles, especially since the stance phase of the sidestep cut is relatively short (mean ± SD, 382 ± 71ms). Another important point is that discrepancies are more evident in muscles with more complex structures (Figures 5-2, 6-1 and 7-1), such as the adductor magnus (which is represented by 4 musculotendinous actuators in the musculoskeletal model). Subsequently, it is difficult to measure the experimental activity of the entire muscle. Nonetheless, EMG-driven methods (114, 175) may provide a more participant-specific approach, which is likely necessary for future work aiming to directly inform clinical decision making (e.g. assessing the effect of certain interventions aiming to change muscular contributions to joint loading).

Since the goal of these investigations were to identify the role of muscle, the relative computational efficiency and robustness of static optimisation provided appropriate justification for use in the present thesis. The physiological plausibility of the simulations was supported by the extensive validation, performed according to current best practice recommendations (113). As an inverse method, the reliability of muscle forces estimated via static optimisation depends on the reliability of the experimental input data (mass/inertial data, kinematics and GRFs) (168). Previously published data (172, 174) suggests that the experimental input data were likely to have sufficient reliability (as described in Chapter 3).

8.2.4 Muscle function

A key component of this thesis was the evaluation of muscle function, where by muscular contributions to joint loading and segment accelerations were determined via GRF decomposition. Whilst this method has several advantages, including accounting for dynamic coupling, it is susceptible to modelling error (155). However, the principle of superposition between computations using experimental GRFs, and foot-ground contact model-derived GRFs was verified. Based on comparison with prior work of walking and running (155), these errors were deemed acceptable for all computations, except for the GRFs during the toe-off period. Subsequently, kinematic data in Chapters 6 and 7 (in which analysis included the toe-off period) was processed with a residual reduction algorithm. This algorithm makes small perturbations to the torso inertial properties and overall kinematics to reduce the dynamic inconsistency between the kinematic and GRF data. Perturbations to torso inertial properties are justified since the torso is modelled as a single rigid body, whilst, in reality, it consists of numerous joints and segments. Perturbations to kinematic data are also justified since these are relatively susceptible to measurement error associated with soft tissue artefact and a lower sampling rate (compared to GRFs). Importantly, these kinematic adjustments were minimal (Appendix II Figure 2), yet allowed a substantial reduction in the superposition error between the experimental and predicted GRFs. However, the superposition error quantifies how well the various forces within the system sum to the total experimental GRF (155), and can therefore only represent the suitability of the rigid contact assumption (49). Subsequently, it is important to recognise that a low superposition error is a necessary but not sufficient condition for this analysis, and gives no representation of the accuracy of the estimates of muscle function or coordination.

Estimates of muscle function are dependent on the foot-ground contact model used (155). The work in the present thesis was based on a five-point foot-ground contact model, which incorporates time-varying kinematic constraints depending on the position of the measured centre of pressure relative to the five modelled contact points (156). Whilst other foot-ground contact models do exist (e.g. (155, 177)), the chosen model is likely more realistic than other single-point and/or unweighted models (155, 178). Further validation of foot-ground contact models is an area for future research. Validation may be provided via comparison of model estimated induced segment accelerations with experimentally measured induced accelerations from electrical stimulation of individual muscles (298, 299). However, these experiments are currently limited to treadmill based experimental protocols, thus their application to sidestep cutting may be limited.

8.2.5 Contact forces

For Chapter 6, estimation of tibiofemoral compartment compressive loading was achieved with the use of a frontal plane equilibrium model at the knee, as other musculoskeletal modelling studies have done (158). Other methods to estimate tibiofemoral compartment loading exist, such as finite element modelling (300) and surrogate contact modelling (301). Although more computationally demanding than the framework used in the present thesis, these methods have certain advantages, such as accounting for different contact geometries and direct modelling of knee ligaments. However, for these contact geometries to be truly participant-specific, imaging data is required which was not obtained in the present work. Additionally, many ligament properties cannot be directly measured, hence need to be estimated which introduces additional uncertainty into calculations (261). In contrast, the frontal plane equilibrium method used in the present work is more computationally efficient, does not introduce additional uncertainty associated with ligament modelling, and has been shown to produce valid estimates of contact forces compared to in-vivo data (302, 303).

The frontal plane equilibrium method is not without limitations, such as the requirement of prior knowledge of the location of the tibiofemoral contact points. These contact points were not determined from in-vivo data, as imaging data was not collected. Instead, the contact point locations were placed on a generic location within the standard musculoskeletal model, and then scaled to each participant based on femoral epicondyle width, a method similar to other studies (158, 280, 281, 304). Prior studies have performed sensitivity analysis, showing the predicted contact forces are relatively robust to contact point locations (107, 158, 160). However, it is unclear how robust muscular contributions to contact forces are to contact point locations. Thus, an additional sensitivity analysis was performed for a single participant, where contact points where perturbed by 20% (corresponding to 4mm) in the frontal plane. This created 4 conditions, where contact points were moved towards each other, away from each other, and in the same direction (medially and laterally). As shown in Appendix III Figure 4, muscular contributions to contact forces were robust to the contact point location changes. Although in-vivo data should be used where available, this sensitivity analysis shows that the conclusions made in Chapter 6 were likely robust to error associated with contact point estimation.

8.3 Future work

Future work will build on the studies presented in this thesis and will attempt to incorporate advancement in methodology. Work is currently underway to combine EMG-hybrid muscle

force prediction techniques (114, 176) with GRF decomposition methods (156). This method would allow reproduction of the analysis in the present thesis, with key muscle activations to be directly informed by participant-specific activation patterns, whilst constraining the optimisation solution space of other muscles where EMG data is not available. This method can account for participant-specific muscle activation and co-contraction strategies. This method can then be used to monitor interventions aiming to retrain neuromuscular activation patterns to facilitate lower ACL and joint contact loading during potentially injurious manoeuvres.

The findings of this thesis also provides direction for investigations which aim to further explore the link between prior HSI and future ACL injury. There is a current preoccupation in the literature to examine and restore function of the previously injured hamstrings whilst little attention is paid to other lower-limb muscles. The current works show many lower-limb muscles, including non-knee-spanning muscles, contribute to knee joint loading during a change-of-direction manoeuvre and that these muscles operate in a complex, interdependent manner. Exploring the impact of prior HSI on muscles/muscle groups other than the hamstrings as well as conducting more detailed biomechanical analyses in this population is a promising next step in this field.

8.4 Summary

In summary, this work has contributed to the knowledge base of how the hamstrings contribute to knee joint loading relative to other lower-limb muscles. These findings have implications for better understanding ACL injury risk. Key muscle groups which may reduce ACL loading during sidestep cutting have been elucidated, whilst consideration to performance requirements and other associated pathologies should provide meaningful information for the development of more effective and targeted interventions. Future work is needed to determine the relationship, if any, between prior HSI and future ACL injury that considers the both knee and non-knee-spanning muscles.

Chapter 9 – References

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Chapter 10 – Appendices

The following section contains appendices for the entire thesis, including supplementary material associated with each publication.

Appendix I: Research portfolio

Publications

1. **Maniar, N,** Shield, A.J, Williams, M.D, Timmins, R.G, & Opar, D.A. (2016) Hamstring strength and flexibility after hamstring strain injury: a systematic review and meta-analysis. *British Journal of Sports Medicine*, *50*(15). 909-920. doi: 10.1136/bjsports-2015-095311.

Contribution statement: NM was responsible for the conception of the project, development and execution of the search strategy, screening of articles, data extraction, qualitative and quantitative analysis, preparation of figures, writing and submission of the manuscript, responding to reviewer feedback and approving the final proof. AS and MW assisted in writing of the manuscript and responding to reviewer feedback. RT assisted in full-text article screening, writing of the manuscript and responding to reviewer feedback. DO contributed to the conception of the project, development of the search strategy, full-text screening, quality assessment, writing of the manuscript and responding to reviewer feedback.

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Approximate percentage contributions – N. Maniar 70%; A.J. Shield 5%; M.D. Williams 5%; R.G. Timmins 5%; D.A. Opar 15%.

I acknowledge that my contribution to the above publication is 70%:

03/12/2017

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Anthony J Shield — Date

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Morgan D Williams — Date

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Ryan Gregory Timmins — Date

2. **Maniar, N,** Schache, A.G, Sritharan, P, & Opar, D.A. Non-knee-spanning muscles contribute to tibiofemoral shear as well as valgus and rotational joint reaction moments during unanticipated sidestep cutting. *Scientific Reports, 8*(1). 2501. doi: 10.1038/s41598-017-19098-9.

Contribution statement: NM was responsible for the conception of the project, data collection and analysis, preparation of figures, interpretation of data, writing and submission of the manuscript and responding to reviewer feedback. AS, PS and DO assisted in the conception of the project, interpretation of data, writing of the manuscript and responding to reviewer feedback.

Approximate percentage contributions – N. Maniar 85%; A.G. Schache 5%; P. Sritharan 5%; D.A. Opar 5%.

I acknowledge that my contribution to the above publication is 85%:

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In review

1. **Maniar, N,** Cole, M.H, Bryant, A.L, & Opar, D.A. Muscle force contributions to anterior cruciate ligament loading. *Sports Medicine*. In review.

Contribution statement: NM was responsible for the conception of the project, literature searching, preparation of figures, interpretation of data, and writing and submission of the manuscript. MC, AB and DO assisted in the conception of the project, interpretation of data, and writing of the manuscript.

Approximate percentage contributions – N. Maniar 85%; M.H. Cole 5%; A.L. Bryant 5%; D.A. Opar 5%.

I acknowledge that my contribution to the above publication is 85%:

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2. **Maniar, N,** Schache, A.G, Cole M.H, & Opar, D.A. Muscle function during sidestep cutting. *Journal of Biomechanics.* In review (minor revisions received).

Contribution statement: NM was responsible for the conception of the project, data collection and analysis, preparation of figures, interpretation of data, and writing and submission of the manuscript. AS assisted in the conception of the project, interpretation of data, and writing of the manuscript. MC assisted in the interpretation of data and writing of the manuscript. DO contributed to the conception of the project, interpretation of data, and writing of the manuscript.

Approximate percentage contributions – N. Maniar 80%; A.G. Schache 10%; M.H. Cole 5%; D.A. Opar 5%.

I acknowledge that my contribution to the above publication is 80%:

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Michael H Cole Date

In preparation

1. **Maniar, N,** Bryant, A.L, Sritharan, P, & Opar, D.A. Muscular contributions to medial and lateral tibiofemoral contact forces during sidestep cutting. *Osteoarthritis and Cartilage.* In preparation.

Contribution statement: NM was responsible for the conception of the project, data collection and analysis, preparation of figures, interpretation of data, and writing and submission of the manuscript. AB assisted in the conception of the project, interpretation of data, and writing of the manuscript. PS assisted in the interpretation of data and writing of the manuscript. DO contributed to the conception of the project, interpretation of data, and writing of the manuscript.

Approximate percentage contributions – N. Maniar 80%; A.L. Bryant 10%; P. Sritharan 5%; D.A. Opar 5%.

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Conferences

1. **Maniar, N,** Hickey, J.T, Timmins, R.G, Beerworth, K.A, & Opar, D.A. Hamstring function and anterior cruciate ligament loading. *Football Federation Australia Medical Conference* – Sydney, September 2016.

Contribution statement: This presentation was based on the work from Chapter 5 (see above for author contributions). The presentation was designed and delivered by NM. JH, RT, KB and DO reviewed the presentation and provided feedback.

2. **Maniar, N,** Shield, A.J, Williams, M.D, Timmins, R.G, & Opar, D.A. Recovery of clinical markers of hamstring function during rehab**.** *Sports Medicine Australia Hamstring Injury Symposium* – Melbourne, October 2016.

Contribution statement: This presentation was based on the work from Chapter 4 (see above for author contributions). The presentation was designed and delivered by NM. AS, MW, RT, and DO reviewed the presentation and provided feedback.

3. **Maniar, N,** Schache, A.G, Beerworth, K.A, & Opar, D.A. Non-knee-spanning muscles contribute to knee joint valgus and shear loading. *International Society of Biomechanics 2017* – Brisbane, July 2017.

Contribution statement: This presentation was based on the work from Chapter 5 (see above for author contributions). The presentation was designed and delivered by NM. AS, KB and DO reviewed the presentation and provided feedback.

Appendix II: Supplementary information to publications

The following section contains supplementary material related to each publication.

Appendix II Table 1. Summary of studies discussed in review.

Ref	Study	Class	n	Gender (% male)	Age	Task	Knee flexion min	Knee flexion max	Weight bearing	Muscle force application	Bundle specific reporting?	Marker of ACL load
(105)	Adouni (2016)	*In-silico*	NA	NR	NA	Knee flexion	0	90	No	Simulated	Yes	ACL force
						Gait	~0#	~5#	Yes	Simulated	No	ACL force
(93)	Arms (1984)	*In-vitro*	17	76	54.4	Knee flexion	0	90	No	Cables	Yes	ACL strain
(92)	DeMorat (2004)	*In-vitro*	13	46	(49-93)	Static	20	20	No	Cables	No	ACL rupture, ATT, valgus°, tibial rotation°
(94)	Draganich (1990)	*In-vitro*	5	NR	64.5 ± 20.6 (38-4)	Knee flexion	0	90	No	Cables	Yes	ACL strain
(88)	Durselen (1995)	*In-vitro*	9	NR	(22-55)	Knee flexion	0	110	No	Cables	Yes	ACL strain
(83)	Elias (2003)	*In-vitro*	6	NR	(67-77)	Knee flexion	20	80	No*	Cables	No	ACL strain
(123)	Flaxman (2017)	*In-vivo*	25	48	29.2 ± 6.7M; 25.6 ± 7.3F	Force-direction	23	23	Yes	In-vivo (voluntary)	No	Valgus moment, internal rotation moment
(119)	Fleming (2001)	*In-vivo*	6	67	(38-56)	Knee flexion	5	45	No	In-vivo (stimulation)	Yes	ACL strain
(89)	Guelich (2016)	*In-vitro*	7	57	69 ± 7	Knee flexion	0	90	No	Cables	Yes	ACL strain, ATT, valgus°, tibial rotation°
(98)	Hirokawa (1992)	*In-vitro*	12	NR	NR	Knee flexion	0	120	No	Cables	No	ATT, tibial rotation°
(95)	Howe (1990)	*In-vivo*	5	100	30 (18-40)	Knee flexion	30	90	No	In-vivo (voluntary)	Yes	ACL strain
(96)	Hsich (1997)	*In-vitro*	15	60	51.9 ± 14.8 (28-76)	Knee flexion	0	120	No*	Cables	Yes	ACL length, ATT, valgus°, tibial rotation°
(27)	Li (1999)	*In-vitro*	10	NR	(42-72)	Knee flexion	0	120	No	Cables	No	ACL force, ATT, tibial rotation°

(91)	Li (2004)	*In-vitro*	18	NR	(52-72)	Knee flexion	0	150	No	Cables	No	ACL force
(121)	Lloyd (2001)	*In-vivo*	10	100	28.9 ± 5.5	Force-direction	40	90	No	In-vivo (voluntary)	No	Valgus moment, internal rotation moment
(106)	Lloyd (2005)	*In-vivo*	11	100	21.3 ± 3.4	Sidestep cutting	27	47	Yes	NA	No	Valgus moment
(86)	MacWilliams (1999)	*In-vitro*	8	62	71 (58-91)	Knee flexion	15	70	Yes	Cables	No	ATT, tibial rotation^{o}, shear force
(18)	Markolf (1990)	*In-vitro*	17	NR	(56-68)	Knee flexion	-5	45	No	Cables	No	ACL force
(87)	Markolf (2004)	*In-vitro*	13	77	48 (29-67)	Knee flexion	-5	120	No	Cables	No	ACL force
(110)	Mesfar (2005)	*In-silico*	NA	NR	NA	Knee flexion	0	90	No	Simulated	No	ACL force, ATT
(109)	Mesfar (2006)	*In-silico*	NA	NR	NA	Knee flexion	0	90	No	Simulated	No	ACL force, ATT
(101)	Mokhtarzadeh (2013)	*In-silico*	8	100	22.9 ± 0.6	Single-leg landing	23	65	Yes	Simulated	No	ACL force
(28)	More (1993)	*In-vitro*	10	NR	70	Squat	0	90	Yes	Cables	No	ACL force, ATT, tibial rotation^{o}
(146)	Morgan (2014)	*In-silico*	6	100	20.5 ± 1.9	Single-leg landing	14	61	Yes	Simulated	No	ACL force
(127)	O'Connor (1993)	*Mathematical model*	NA	NR	NA	Knee flexion	0	140	No	Simulated	No	ACL force
(103)	Pandy (1997)	*In-silico*	NA	NR	NA	Knee flexion	0	90	No	Simulated	No	ACL force
(90)	Renstrom (1986)	*In-vitro*	7	NR	60 (37-81)	Knee flexion	0	120	No	Cables	Yes	ACL strain
(122)	Serpell (2015)	*In-vivo*	5	100	24.9 ± 4.1	Single-leg step up	NR	NR	Yes	In-vivo (voluntary)	No	ACL length, ATT, valgus^{o}, tibial rotation^{o}
(104)	Shelburne (1998)	*In-silico*	5	100	26 ± 3	Squat	0	90	Yes	Simulated	No	ACL force, shear force

(108)	Shelburne (2005)	*In-silico*	5	100	26 ± 3	Gait	~3[#]	~35[#]	Yes	Simulated	No	ACL force, shear force
(97)	Sherbondy (2003)	*In-vivo*	12	58	30.6 (18-43)	Dorsi-flexion	30	30	No	In-vivo (passive)	No	ATT
		In-vitro	4	NR	74 (70-78)	Dorsi-flexion	30	30	No	Passive forces	No	ATT
(107)	Sritharan (2012)	*In-silico*	8	100	26 ± 4	Gait	~3[#]	~35[#]	Yes	Simulated	No	Valgus moment
(84)	Withrow (2006)	*In-vitro*	11	45	70.8 ± 19.3	Single-leg landing	25	31	Yes	Cables	Yes	ACL strain
(85)	Withrow (2008)	*In-vitro*	10	40	60.3 ± 23.6	Single-leg landing	25	31	Yes	Cables	Yes	ACL strain, ATT, valgus[o], tibial rotation[o]

Abbreviations: Ref, reference; ACL, anterior cruciate ligament; ATT, anterior tibial translation; NA, not applicable; NR, not reported.

Age data is presented is mean, mean ± standard deviation and/or range (min-max) depending on data availability. NA is given for studies that used a modelling approaches where a single model was used.

[M]Males; [F]Females; [#]Estimated based on normative gait data (305); *Weight bearing was simulated but with insufficient magnitude to reflect realistic bodyweights; [o]Joint angle in degrees.

In-vivo muscle force were generated as either voluntary, voluntary contraction; passive, passive muscle forces; stimulation, contraction produced via electrical stimulation.

Simulated muscle force application involves estimation via optimisation techniques, or specified at specific forces by investigators.

All studies that reported data specific to each ACL bundle included the anteromedial bundle. Two studies (96, 105) also reported data on the posterolateral bundle.

Appendix II Table 2. Modified quality assessment tool derived from Downs and Black (224).

Category	Item	Question
Reporting	1	Is the hypothesis/aim/objective of the study clearly described?
	2	Are the main outcomes to be measured clearly described in the Introduction or Methods section?
	3	Are the characteristics of the patients included in the study clearly described?
	5	Are the distributions of the principal confounders in each group of subjects to be compared clearly described?
	6	Are the main findings of the study clearly described?
	7	Does the study provide estimates of the random variability in the data for the main outcomes?
	10	Have actual probability values (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001
External Validity	11	Were the subjects asked to participate in the study representative of the entire population from which they were recruited?
	12	Were those subjects who were prepared to participate representative of the entire population of which they were recruited?
Internal Validity (bias)	16	If any of the results of the study were based on "data dredging", was this made clear?
	18	Were the statistical tests used to assess the main outcomes appropriate?
	20	Were the main outcome measures used accurate (valid and reliable)?
Internal Validity (confounding)	21	Were the patients in the different intervention groups (trials and cohorts studies) or cases and controls (case control studies) recruited from the same population?
	25	Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?
Power	27	Did the study have a calculation of power and was this met?
Additional Internal Validity (bias)	28*	Was the diagnosis of injury appropriate?

Additional Internal Validity (confounding)	29[#]	Was the rehabilitation of participants controlled and/or reported?

*Item added by authors with assessment scoring, 2 points if injury of all participants was diagnosed by clinical exam (or clinical notes from diagnosing practitioner obtained) and investigated by imaging, 1 point if diagnosis was made by clinical exam (or clinical notes from diagnosing practitioner provided) or imaging, 0 points if diagnosis was made by self-report, questionnaire, clinical criteria or unclear methods of diagnosis were provided. [#]Item added by current authors with assessment scoring, 2 points if rehabilitation was reported (described or referenced) and controlled or measures were taken at initial exam (prior to rehabilitation intervention), 1 point if rehabilitation was reported but not controlled or controlled but not reported, 0 points if rehabilitation was not reported or controlled.

Appendix II Table 3. Concentric knee flexor isokinetic strength in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
60°/sec peak torque (Nm)									
Brockett	Unclear	9	114 ± 24	123 ± 25	-9	[-32, 14]	-7	-0.37	[-1.30, 0.56]
Tol	21 (7-43)	81	114 ± 22	122 ± 22^	-8	[-15, -1]	-7	-0.36	[-0.68, -0.05]
Mackey	<365	9	97 ± 12	95 ± 13	2	[-10, 14]	2	0.16	[-0.77, 1.09]
O'Sullivan	<365	19	119 ± 29	132 ± 29#	-13	[-28, 2]	-10	-0.45	[-0.96, 0.06]
Opar	161 ± 132	13	132 ± 21	146 ± 15	-14	[-28, 0]	-10*	-0.77	[-1.56, 0.03]
O'Sullivan	<730	7	76 ± 13	70 ± 10	6	[-6, 18]	9	0.52	[-0.55, 1.58]
Croisier	60-365	26	No data	No data	No data	-	-11*	-	-
Silder	150- 690	18	No data	No data	No data	-	8	-	-
60°/sec relative peak torque (Nm/kg)									
Sanfilippo	17-49	25	1.2 ± 0.3	1.3 ± 0.3	-0.1	[-0.27, 0.07]	-8	-0.33	[-0.89, 0.22]
	199-231	25	1.3 ± 0.3	1.3 ± 0.3	0.0	[-0.16, 0.16]	0	0.00	[-0.55, 0.55]
Sole	109 ± 106	15	1.5 ± 0.4	1.6 ± 0.3	-0.1	[-0.35, 0.15]	-6	-0.28	[-1.00, 0.44]
Arumugam	147 ± 121	17	1.5 ± 0.4	1.6 ± 0.3	-0.1	[-0.37, 0.17]	-6*	-0.25	[-0.92, 0.42]
O'Sullivan	<365	19	1.5 ± 0.3	1.6 ± 0.3#	-0.1	[-0.25, 0.05]	-6	-0.33	[-0.84, 0.18]
O'Sullivan	<730	7	1.3 ± 0.2	1.2 ± 0.2	0.1	[-0.11, 0.31]	8	0.50	[-0.56, 1.56]
Croisier	60-365	23	1.5	1.7	-0.2	-	-12*	-	-
180°/sec peak torque (Nm)									
Opar	161 ± 132	13	109 ± 13	119 ± 12	-10	[-20, 0]	-8*	-0.80	[-1.60, 0.00]

Mackey	<365	9	81 ± 20	83 ± 14	-2	[-18, 14]	-2	-0.12	[-1.04, 0.81]
O'Sullivan	<365	19	101 ± 20	103 ± 20[#]	-2	[-12, 8]	-2	-0.10	[-0.61, 0.41]
O'Sullivan	<730	7	62 ± 6	54 ± 8	8	[0, 15]	15	1.13	[0.00, 2.26]
180°/sec relative peak torque (Nm/kg)									
O'Sullivan	<365	19	1.2 ± 0.2	1.3 ± 0.2[#]	-0.1	[-0.20, 0.00]	-8	-0.50	[-1.01, 0.01]
O'Sullivan	<730	7	1.0 ± 0.1	0.9 ± 0.2	0.1	[-0.07, 0.27]	11	0.63	[-0.44, 1.71]
240°/sec peak torque (Nm)									
Croisier	60-365	26	No data	No data	No data	-	-10*	-	-
240°/sec relative peak torque (Nm/kg)									
Sanfilippo	17-49	25	0.7 ± 0.2	0.8 ± 0.2	-0.1	[-0.21, 0.01]	-13	-0.50	[-1.06, 0.06]
	199-231	25	0.8 ± 0.2	0.9 ± 0.2	-0.1	[-0.21, 0.01]	-11	-0.50	[-1.06, 0.06]
Croisier	60-365	23	1.1	1.2	-0.1	-	-8	-	-
300°/sec peak torque (Nm)									
Tol	21 (7-43)	80	95 ± 33	91 ± 17^	4	[-4, 12]	4	0.15	[-0.16, 0.46]
O'Sullivan	<365	19	93 ± 18	92 ± 17[#]	1	[-8, 10]	1	0.06	[-0.45, 0.57]
O'Sullivan	<730	7	61 ± 6	59 ± 9	2	[-6, 10]	3	0.26	[-0.79, 1.31]
300°/sec relative peak torque (Nm/kg)									
O'Sullivan	<365	19	1.1 ± 0.2	1.1 ± 0.2[#]	0.0	[-0.10, 0.10]	0	0.00	[-0.51, 0.51]
Lee	578 ± 365	14	1.0 ± 0.2	1.0 ± 0.2	0.0	[-0.15, 0.15]	0	0.00	[-0.74, 0.74]
O'Sullivan	<730	7	1.0 ± 0.1	1.0 ± 0.1	0.0	[-0.10, 0.10]	0	0.00	[-1.05, 1.05]

Negative differences indicate that the outcome variable of interest was lesser in the injured leg compared to the contralateral leg.
Included in review but excluded from this table due to: no contralateral leg comparisons: Jonhagen *et al.*; Insufficient data: Dauty *et al.*; Prone position: Worrell *et al.*
^Contralateral legs did not have same numbers as injured (60°/sec, n = 79; 300°/sec, n = 78); [#]Contralateral legs were pooled with control group legs (O'Sullivan *et al.*, total legs *n* = 69); *Statistically significant difference ($p < 0.05$); SD, standard deviation.

Appendix II Table 4. Eccentric knee flexor strength in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*N*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
30°/sec peak torque (Nm)									
Mackey	<365	9	130 ± 39	143 ± 35	-13	[-47, 21]	-9	-0.35	[-1.28, 0.58]
Croisier	60-365	26	No data	No data	No data	-	-22*	-	-
30°/sec relative peak torque (Nm/kg)									
Croisier	60-365	23	1.4	1.8	-0.4	-	-22*	-	-
60°/sec peak torque (Nm)									
Tol	21 (7-43)	74	170 ± 37	174 ± 39	-4	[-16, 8]	-2	-0.11	[-0.43, 0.22]
Opar	161 ± 132	13	167 ± 30	185 ± 25	-18	[-40, 0]	-10*	-0.65	[-1.44, 0.14]
60°/sec relative peak torque (N/m/kg)									
Sole	109 ± 106	15	2.5 ± 0.6	2.7 ± 0.5	-0.2	[-0.60, 0.20]	-7	-0.36	[-1.08, 0.36]
Arumugam	147± 121	17	2.4 ± 0.5	2.5 ± 0.5	-0.1	[-0.44, 0.24]	-4	-0.20	[-0.87, 0.47]
Doherty[I]	261 ± 195	16	1.6 ± 0.4	1.7 ± 0.4	-0.1	[-0.38, 0.18]	-6	-0.25	[-0.95, 0.45]
Doherty[III]	261 ± 195	26	1.5 ± 0.3	1.5 ± 0.2	0	[-0.14, 0.14]	0	0.00	[-0.54, 0.54]
120°/sec peak torque (Nm)									
Croisier	60-365	26	No data	No data	No data	-	-24*	-	-
120°/sec relative peak torque (Nm/kg)									
Croisier	60-365	23	1.4	1.8	-0.4	-	-22*	-	-
180°/sec peak torque (Nm)									
Opar	161 ± 132	13	164 ± 30	184 ± 22	-20	[-40, 0]	-11*	-0.76	[-1.56, 0.04]
Doherty[I]	261 ± 195	16	1.7 ± 0.4	1.5 ± 0.3	0.2	[-0.04, 0.44]	13	0.57	[-0.14, 1.27]

Doherty[III]	261 ± 195	26	1.7 ± 0.4	1.6 ± 0.3	0.1	[-0.09, 0.29]	6	0.28	[-0.26, 0.83]
300°/sec relative peak torque (Nm/kg)									
Lee	578 ± 365	14	1.8 ± 0.3	2.0 ± 0.4	-0.2	[-0.46, 0.06]	-10*	-0.57	[-1.32, 0.19]
Nordic hamstring exercise (N)									
Opar	171	20	295 ± 100	345 ± 116	-50	[-117, 17]	-14*	-0.46	[-1.09, 0.17]
Timmins	291 ± 115	16	289 ± 85	341 ± 100	-52	[-116, 12]	-15*	-0.56	[-1.27, 0.15]
Opar	134 [MED]	17	298 ± 90	311 ± 83	-13	[-71, 45]	-4	-0.15	[-0.82, 0.52]

Negative differences indicate that the outcome variable of interest was lesser in the injured leg compared to the contralateral leg.
Included in review but excluded from this table due to: no contralateral leg comparisons: Jonhagen *et al.*; Insufficient data: Dauty *et al.*; Prone position: Worrell *et al.*
^Contralateral legs did not have same numbers as injured (60°/sec, n = 73); *Statistically significant difference ($p < 0.05$); [MED] = median; [I] Division one athletes; [III] Division three athletes; SD, standard deviation;

Appendix II Table 5. Knee flexor isometric strength in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
Long length (0° hip, 0-15° knee) (Nm)									
Askling sprinters	2	18	36 ± 15	95 ± 18	-59*	[-70, -48]	-62	-3.56	[-4.61, -2.51]
	10	18	66 ± 15	98 ± 20	-32*	[-44, -20]	-33	-1.81	[-2.59, -1.03]
	21	18	80 ± 25	93 ± 26	-13*	[-30, 4]	-14	-0.51	[-1.17, 0,15]
	42	18	93 ± 19	102 ± 20	-9*	[-22, 4]	-9	-0.46	[-1.12, 0.20]
Askling dancers	2	15	56 ± 19	69 ± 17	-13*	[-26, 0]	-19	-0.72	[-1.46, 0.02]
	10	15	66 ± 18	72 ± 17	-6*	[-19, 7]	-8	-0.34	[-1.06, 0.38]
	21	15	70 ± 17	73 ± 17	-3	[-15, 9]	-4	-0.18	[-0.89, 0.54]
	42	15	70 ± 19	71 ± 18	-1	[-14, 12]	-1	-0.05	[-0.77, 0.66]
Long length (0° hip, 0-15° knee) (N)									
Reurink	3	74	175 ± 79	246 ± 60	-71	[-94, -48]	-29	-1.01	[-1.35, -0.67]
	10	76	210 ± 68	241 ± 54	-31	[-51, -11]	-13	-0.50	[-0.83, -0.18]
	185	72	253 ± 68	255 ± 63	-2	[-23, 19]	-1	-0.03	[-0.36, 0.30]
Timmins	237	16	237 ± 53	263 ± 51	-26	[-62, 10]	-10	-0.5	[-1.20, 0.20]
Short length (0° hip, 90° knee) (N)									
Reurink	3	74	160 ± 55	195 ± 38	-35	[-50, -20]	-18	-0.74	[-1.07, -0.41]
	10	76	180 ± 50	198 ± 42	-18	[-33, -3]	-9	-0.39	[-0.71, -0.07]
	185	72	194 ± 42	199 ± 39	-5	[-18, 8]	-3	-0.12	[-0.45, 0.20]

Negative differences indicate that the isometric strength of the injured legs were less than the uninjured contralateral legs.

*Statistically significant difference ($p < 0.05$); SD, standard deviation.

Appendix II Table 6. Conventional H:Q ratio (expressed as a %) collected during seated isokinetic dynamometry in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
60:60°/sec									
Croisier	61-365	23	53 ± 14	58 ± 6	-5	[-11, 1]	-9	-0.46	[-1.05, 0.12]
Croisier	61-365	26	55 ± 14	59 ± 5	-4	[-10, 2]	-7	-0.38	[-0.93, 0.17]
Sole	109 ± 106	15	59 ± 11	60 ± 9	-1	[-8, 6]	-2	-0.10	[-0.82, 0.62]
Doherty[I]	261 ± 195	16	76 ± 35	80 ± 28	-4	[-26, 18]	-5	-0.13	[-0.82, 0.57]
Doherty[III]	261 ± 195	26	81 ± 45	99 ± 81	-18	[-54, 18]	-18	-0.27	[-0.82, 0.27]
Mackey	<365	9	53 ± 5	51 ± 5	2	[-3, 7]	4	0.40	[-0.53, 1.33]
O'Sullivan	<365	19	62 ± 10	69 ± 10[#]	-7*	[-12, -2]	-10	-0.70	[-1.22, -0.18]
Dauty	328 ± 198	11	62 ± 13	67 ± 9[#]	-5	[-13, 3]	-7	-0.51	[-1.17, 0.16]
O'Sullivan	<730	7	55 ± 9	52 ± 6	3	[-5, 11]	6	0.39	[-0.67, 1.45]
Silder	152-699	18	No data	No data	6	-	-	-	-
Brockett	Unclear	9	55	58	-3	-	-5	-	-
180:180°/sec									
Doherty[I]	261 ± 195	16	89 ± 42	90 ± 37	-1	[-28, 26]	1	-0.03	[-0.72, 0.67]
Doherty[III]	261 ± 195	26	110 ± 74	110 ± 107	-0	[-50, 50]	0	0.00	[-0.54, 0.54]
Mackey	<365	9	63 ± 7	61 ± 4	2	[-3, 7]	3	0.35	[-0.58, 1.28]
O'Sullivan	<365	19	69 ± 10	71 ± 10[#]	-2	[-7, 3]	-3	-0.20	[-0.71, 0.31]
O'Sullivan	<730	7	61 ± 9	55 ± 7	6	[-3, 15]	11	0.74	[-0.39, 1.86]
240:240°/sec									

Croisier	61-365	23	54 ± 15	59 ± 7	-5	[-12, 2]	8	-0.43	[-1, 0]
Croisier	61-365	26	56 ± 12	60 ± 5	-4	[-9, 1]	7	-0.44	[-1, 0]
300:300°/sec									
O'Sullivan	<365	19	73 ± 10	75 ± 10[#]	-2	[-7, 3]	-3	-0.20	[-0.71, 0.31]
Lee	578 ± 365	14	60 ± 10	60 ± 10	0	[-7, 7]	0	0.00	[-0.74, 0.74]
O'Sullivan	<730	7	75 ± 9	75 ± 7	0	[-8, 8]	0	0.00	[-1.05, 1.05]

Negative differences indicate that the H:Q were lower in previously injured legs compared to the uninjured contralateral legs.
[#]Contralateral legs were pooled with control group legs (O'Sullivan *et al.*, total legs *n* = 69; Dauty *et al.*, total legs *n* = 45); *Statistically significant difference ($p < 0.05$); [I] Division one athletes; [III] Division three athletes; SD, standard deviation.

Appendix II Table 7. Functional H:Q ratio (expressed as a %) collected during seated isokinetic dynamometry in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
30:60°/sec									
Mackey	<365	9	69 ± 15	76 ± 17	-7	[-22, 8]	-9	-0.44	[-1.37, 0.50]
30:180°/sec									
Mackey	<365	9	101 ± 27	107 ± 34	-6	[-34, 22]	-6	-0.20	[-1.12, 0.73]
30:240°/sec									
Sanfilippo	17-49	13	130 ± 26	162 ± 31	-32*	[-54, -10]	-20	-1.12	[-1.95, -0.29]
	199-231	13	139 ± 26	146 ± 15	-7*	[-23, 9]	-5	-0.33	[-1.10, 0.44]
Croisier	61-365	15	75 ± 23	90 ± 16	-15*	[-29, -1]	-17	-0.76	[-1.50, -0.02]
Croisier	61-365	26	73 ± 24	90 ± 16	-17*	[-28, -6]	-19	-0.83	[-1.40, -0.27]
60:60°/sec									
Sole	109 ± 106	15	96 ± 12	101 ± 14	-5	[-14, 4]	-5	-0.38	[-1.11, 0.34]
Arumugam	147 ± 121	17	88 ± 14	90 ± 16	-2	[-12, 8]	-2	-0.13	[-0.81, 0.54]
Doherty[I]	261 ± 195	16	111 ± 35	114 ± 38	-3	[-28, 22]	-3	-0.08	[-0.78, 0.61]
Doherty[III]	261 ± 195	26	130 ± 76	125 ± 72	5	[-35, 45]	4	0.07	[-0.48, 0.61]
Dauty	328 ± 198	11	65 ± 21	80 ± 15[#]	-15*	[-28, -2]	-19	-0.92	[-1.60, -0.24]
180:180°/sec									
Doherty[I]	261 ± 195	16	149 ± 101	152 ± 100	-3	[-73, 67]	-2	-0.03	[-0.72, 0.66]
Doherty[III]	261 ± 195	26	242 ± 213	254 ± 223	-12	[-131, 107]	-5	-0.06	[-0.60, 0.49]
300:300°/sec									

Lee	578 ± 365	14	110 ± 20	120 ± 20	-10*	[-25, 5]	-8	-0.50	[-1.25, 0.25]

Negative differences indicate the functional H:Q was lower in previously injured legs compared to the contralateral uninjured leg.

[#]Contralateral legs were pooled with control group legs (Dauty *et al.*, total legs $n = 45$); *Statistically significant difference ($p < 0.05$); [I] Division one athletes; [III] Division three athletes; SD, standard deviation.

Appendix II Table 8. Knee flexor angle of peak torque (reported in degrees from full knee extension) in previously injured compared to contralateral uninjured legs during seated isokinetic dynamometry.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
60°/sec concentric									
Brockett	Unclear	9	41 ± 8	30 ± 5	12*	[5, 17]	36	1.65	[0.58, 2.72]
Sanfilippo	17-49	22	40 ± 15	40 ± 14	0	[-9, 9]	0	0.00	[-0.59, 0.59]
	199-231	22	29 ± 12	30 ± 15	-1	[-9, 7]	-3	-0.07	[-0.66, 0.52]
Mackey	<365	9	59 ± 15	59 ± 9	0	[-12, 12]	0	0.00	[-0.92, 0.92]
Silder	150-690	18	No data	No data	2	-	-	-	-
240°/sec concentric									
Sanfilippo	17-49	22	43 ± 11	45 ± 10	2	[-8, 4]	-4	-0.19	[-0.78, 0.40]
	199-231	22	40 ± 9	42 ± 8	2	[-7, 3]	-5	-0.24	[-0.83, 0.36]
300°/sec concentric									
Lee	578 ± 365	14	46 ± 5	51 ± 7	-5	[-10, 0]	-10	-0.82	[-1.59, -0.05]
30°/sec eccentric									
Mackey	<365	9	40 ± 19	26 ± 3	14*	[1, 27]	54	1.03	[0.05, 2.01]
300°/sec eccentric									
Lee	578 ± 365	14	59 ± 20	50 ± 16	9	[-4, 22]	18	0.50	[-0.26, 1.25]

Negative differences indicate that the angle of peak torque of the injured legs were at a smaller knee flexion angle (longer muscle lengths) than the uninjured contralateral legs, 0° = full extension.
*Statistically significant difference ($p < 0.05$); SD, standard deviation.

Appendix II Table 9. Range of motion in passive and active straight leg raise tests (reported in degrees from neutral hip position) in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
Passive									
Askling sprinters	2	18	54 ± 16	88 ± 14	-34*	[-44, -24]	-39	-2.26	[-3.10, -1.43]
	10	18	71 ± 14	89 ± 15	-18*	[-27, -9]	-20	-1.24	[-1.95, -0.53]
	21	18	81 ± 14	90 ± 15	-9*	[-18, 0]	-10	-0.62	[-1.29, 0.05]
	42	18	84 ± 15	90 ± 16	-6*	[-16, 4]	-7	-0.39	[-1.05, 0.27]
Askling dancers	2	15	95 ± 14	119 ± 19	-24*	[-36, -12]	-20	-1.44	[-2.24, -0.64]
	10	15	104 ± 14	119 ± 17	-15 *	[-26, -4]	-13	-0.96	[-1.72, -0.21]
	21	15	106 ± 14	118 ± 18	-12 *	[-24, 0]	-10	-0.74	[-1.48, 0.00]
	42	15	108 ± 19	118 ± 19	-10 *	[-24, 4]	-8	-0.53	[-1.25, 0.20]
Reurink	3	80	57 ± 10	61 ± 9	-4	[-7, -1]	-7	-0.42	[-0.73, -0.11]
	10	80	59 ± 9	61 ± 8	-2	[-5, 1]	-3	-0.23	[-0.55, 0.08]
	185	72	60 ± 9	59 ± 8	1	[-2, 4]	2	0.12	[-0.21, 0.44]
Silder^{PATS}	4^{Med}	16	63 ± 18	81 ± 14	-18^	[-29, -7]	-22	-1.12	[-1.86, -0.37]
	25 ± 6	13	83 ± 13	86 ± 14	-3	[-13, 7]	-3	-0.22	[-0.99, 0.55]
Silder^{PRES}	6^{Med}	13	70 ± 16	80 ± 15	-10	[-22, 2]	-13	-0.64	[-1.43, 0.14]
	29 ± 11	11	80 ± 13	78 ± 13	2	[-9, 13]	3	0.15	[-0.68, 0.99]
Askling	55 ± 25	11	91 ± 18	91 ± 19	0	[-15, 15]	0	0.00	[-0.84, 0.84]
Active									

Askling[#]	55 ± 25	11	110 ± 14	119 ± 12	-9*	[-20, 2]	-8	-0.69	[-1.55, 0.17]
Hennessy	<365	18	78 ± 11	78 ± 8	0	[-6, 6]	0	0.00	[-0.65, 0.65]

Negative differences indicate that the range of motion of the injured legs were less than the uninjured contralateral legs, 0° = neutral hip.
[PATS], Progressive agility and trunk stabilisation rehabilitation protocol; [PRES], Progressive running and eccentric strengthening rehabilitation protocol; [Med], Median
[#]Askling H-test is an explosive straight leg raise; *Statistically significant difference ($p < 0.05$); ^ = Statistically significant ($p<0.05$), not calculated by original authors, but performed by the current investigators; SD, standard deviation.

Appendix II Table 10. Range of motion in passive and active knee extension tests (reported in degrees from full knee extension) in previously injured and contralateral uninjured legs.

Author	Days since injury (mean ± SD)	*n*	Injured leg (mean ± SD)	Contralateral leg (mean ± SD)	Mean difference		Percent difference (%)	Effect size	
					Mean	95%CI [Lower, Upper]		Cohen's *d*	95%CI [Lower, Upper]
Passive									
Reurink	3 [Med]	50	132 ± 16	142 ± 13	-10	[-16, -4]	-7	-0.69	[-1.09, -0.28]
Silder[PATS]	4[Med]	16	146 ± 20	146 ± 17	0	[-13, 13]	0	0.00	[-0.69, 0.69]
	25 ± 6	13	167 ± 9	167 ± 9	0	[-7, 7]	0	0.00	[-0.77, 0.77]
Silder[PRES]	6 [Med]	13	145 ± 21	141 ± 22	4	[-13, 21]	3	0.19	[-0.58, 0.96]
	29 ± 11	11	162 ± 9	159 ± 11	3	[-5, 11]	2	0.30	[-0,54, 1.14]
Worrell	<540	16	143 ± 11	148 ± 13	-5*	[-13, 3]	-3	-0.42	[-1.12, 0.29]
Lowther	<365	9	No data	No data	-6*	-	-	-	-
Active									
Reurink	3 [Med]	80	128 ± 15	140 ± 11	-12	[-16, -8]	-9	-0.91	[-1.24, -0.59]
	10	80	134 ± 13	139 ± 10	-5	[-9, -1]	-4	-0.43	[-0.74, -0.12]
	185	72	140 ± 12	140 ± 11	0	[-4, 4]	0	0.00	[-0.33, 0.33]
Silder[PATS]	4 [Med]	16	159 ± 21	157 ± 10	2	[-9, 13]	1	0.12	[-0.57, 0.82]
	25 ± 6	13	162 ± 10	162 ± 8	0	[-7, 7]	0	0.00	[-0.77, 0.77]
Silder[PRES]	6 [Med]	13	154 ± 9	151 ± 12	3	[-5, 11]	2	0.28	[-0.49, 1.06]
	29 ± 11	11	157 ± 11	154 ± 12	3	[-7, 13]	2	0.26	[-0.58, 1.10]
Sole	108 ± 105	15	159 ± 9	160 ± 19	-1	[-12, 10]	-1	-0.07	[-0.78, 0.65]

Negative differences indicate that the range of motion of the injured legs were less than the uninjured contralateral legs, 0° = full extension.
Included in review but excluded from this table due to: no contralateral leg comparisons: O'Sullivan *et al.*
[PATS], Progressive agility and trunk stabilisation rehabilitation protocol; [PRES], Progressive running and eccentric strengthening rehabilitation protocol; [Med], Median; *Statistically significant difference ($p < 0.05$); SD, standard deviation.

Appendix II Table 11. Sensitivity analysis for pooled estimate with heterogeneity (≥30%).

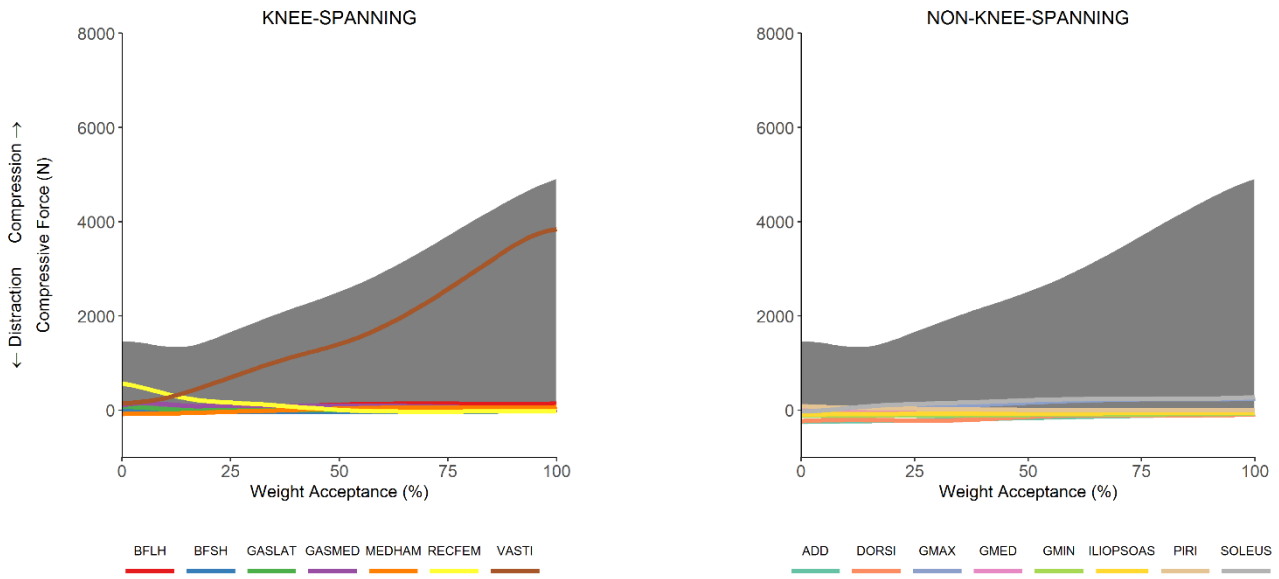
	Pooled					Post-removal		
	Effect size		Heterogeneity			Effect size		Heterogeneity
Variable (subgroup)	Cohen's d	95%CI [Lower, Upper]	I^2 (%)	95%CI [Lower, Upper]	Study omitted	Cohen's d	95%CI [Lower, Upper]	I^2 (%)
PSLR $_{(<10)}$	-1.12	[-1.76, -0.48]	81	[55, 92]	Askling 2006a	-0.79	[-1.26, -0.33]	55
PSLR $_{(10\text{-}20)}$	-0.74	[-1.38, -0.09]	76	[21, 93]	Reurink 2015	-1.08	[-1.60, -0.56]	0
AKE $_{(<10)}$	-0.23	[-1.02, 0.55]	84	[53, 95]	Reurink 2015	0.18	[-0.33, 0.70]	0
AKE $_{(10\text{-}30)}$	-0.19	[-0.63, 0.24]	33	[0, 93]	Reurink 2015	0.11	[-0.45, 0.68]	0
PKE $_{(<10)}$	-0.24	[-0.81, 0.32]	63	[0, 90]	Reurink 2015	0.08	[-0.43, 0.60]	0
AngPT $_{(60)}$	0.48	[-0.53, 1.50]	73	[11, 93]	Brocket 2004	0.00	[-0.50, 0.50]	0
Concentric $_{(180)}$	-0.05	[-0.72, 0.62]	60	[0, 87]	O'Sullivan 2009	-0.26	[-0.68, 0.14]	3
Eccentric $_{(180)}$	-0.06	[-0.68, 0.80]	70	[0, 91]	Opar 2013	0.38	[-0.05, 0.81]	0

PSLR, passive straight leg raise; AKE, active knee extension; PKE, passive knee extension; AngPT, angle of peak torque; $_{<10}$, less than 10 days post injury; $_{10\text{-}20}$, between 10 and 20 days post injury; $_{10\text{-}30}$, between 10 and 30 days post injury; $_{60}$, concentric isokinetic velocity of 60°/sec; $_{180}$, isokinetic velocity of 180°/sec.
Askling 2006a refers to the cohort of sprinters.

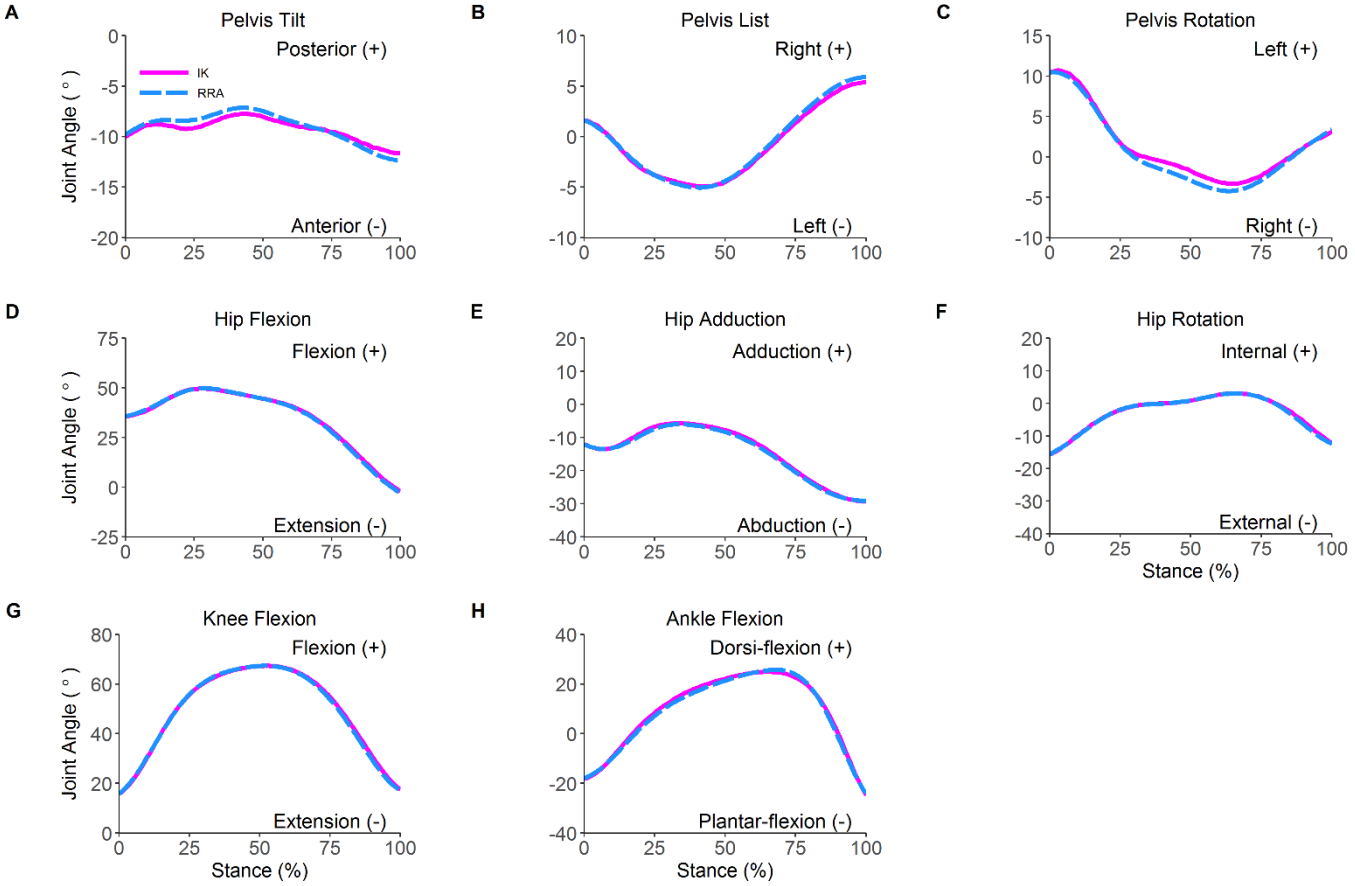
Appendix II Table 12. Functional groups of musculotendinous actuators used in the present study.

Functional group	Muscles	Musculotendinous actuators*
ADD	Adductor brevis	addbrev
	Adductor longus	addlong
	Adductor magnus	addmagProx
		addmagMid
		addmagDist
		addmagIsch
DORSI	Extensor digitorum longus	edl
	Extensor hallucis longus	ehl
	Tibialis anterior	tibant
GAS[#]	Lateral gastrocnemius	gaslat
	Medial gastrocnemius	gasmed
GMAX	Gluteus maximus	glmax1
		glmax2
		glmax3
GMED	Gluteus medius	glmed1
		glmed2
		glmed3
GMIN	Gluteus minimus	glmin1
		glmin2
		glmin3
HAM[#]	Biceps femoris long head	bflh
	Semimembranosus	semimem
	Semitendinosus	semiten
ILIOPSOAS	Iliacus	iliacus
	Psoas major	psoas
MEDHAM	Semimembranosus	semimem
	Semitendinosus	semiten
VASTI	Vastus Intermedius	vasint
	Vastus Lateralis	vaslat
	Vastus Medialis	vasmed

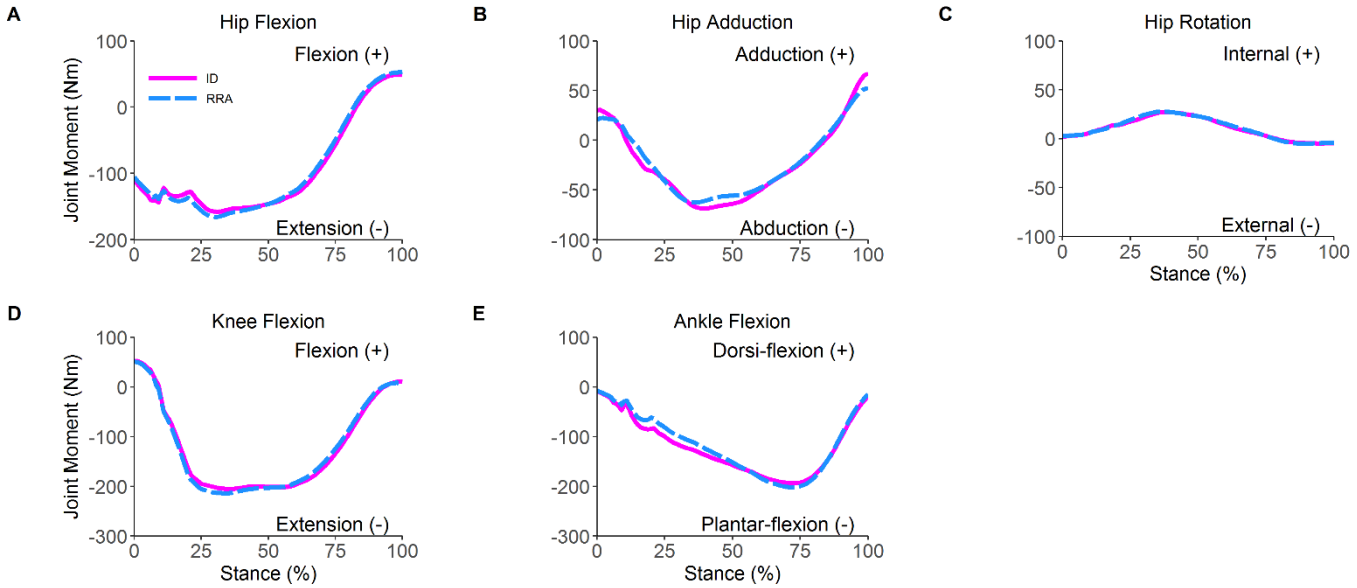
*Actuator names taken from musculoskeletal model; [#]Grouping only applied for chapter 7.



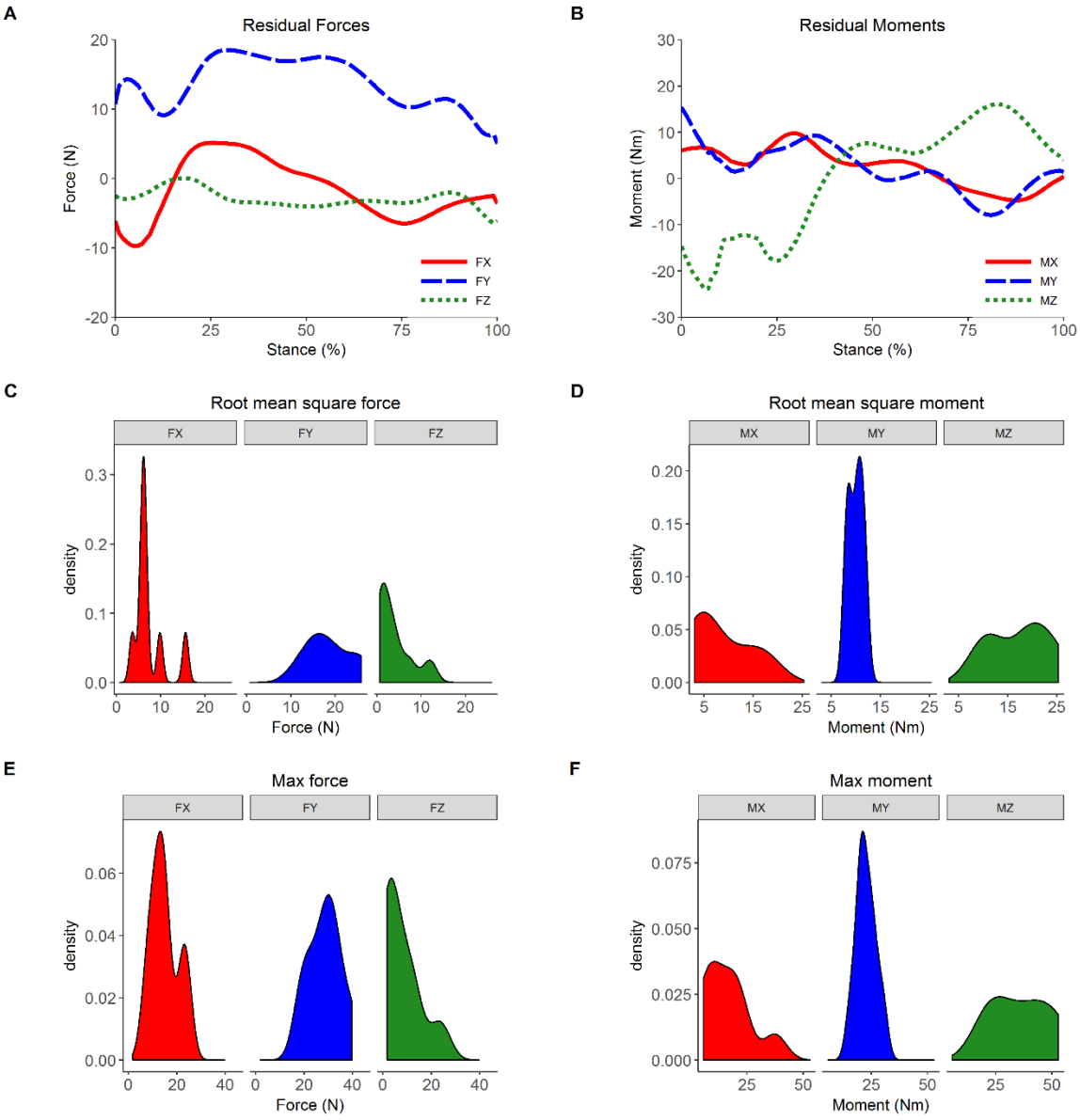
Appendix II Figure 1. Muscular contributions to the knee compressive force during the weight acceptance phase of the 45º unanticipated sidestep cut. The first column shows knee-spanning muscles, the second column shows non-knee-spanning muscles. Note that the shaded grey represents the experimental value (net value accounting for all forces) for the knee compressive force. BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOLEUS, soleus.



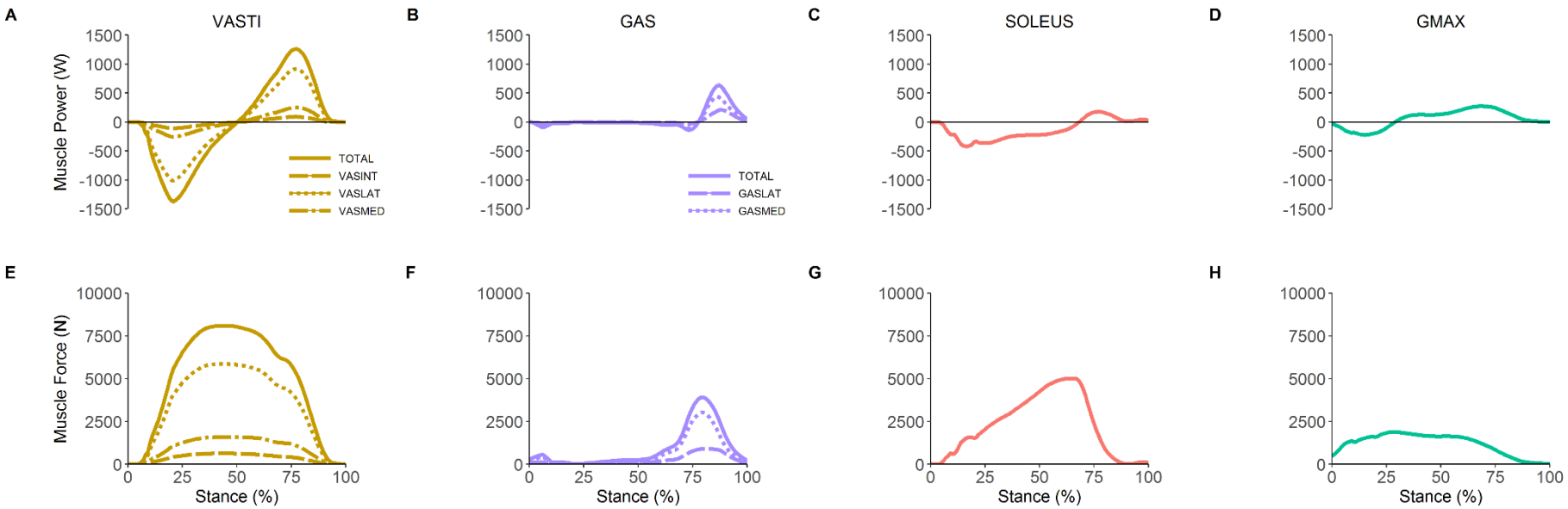
Appendix II Figure 2. Joint angles computed via inverse kinematics (IK) and the residual reduction algorithm (RRA) during the stance phase of a 45° unanticipated sidestep cut.



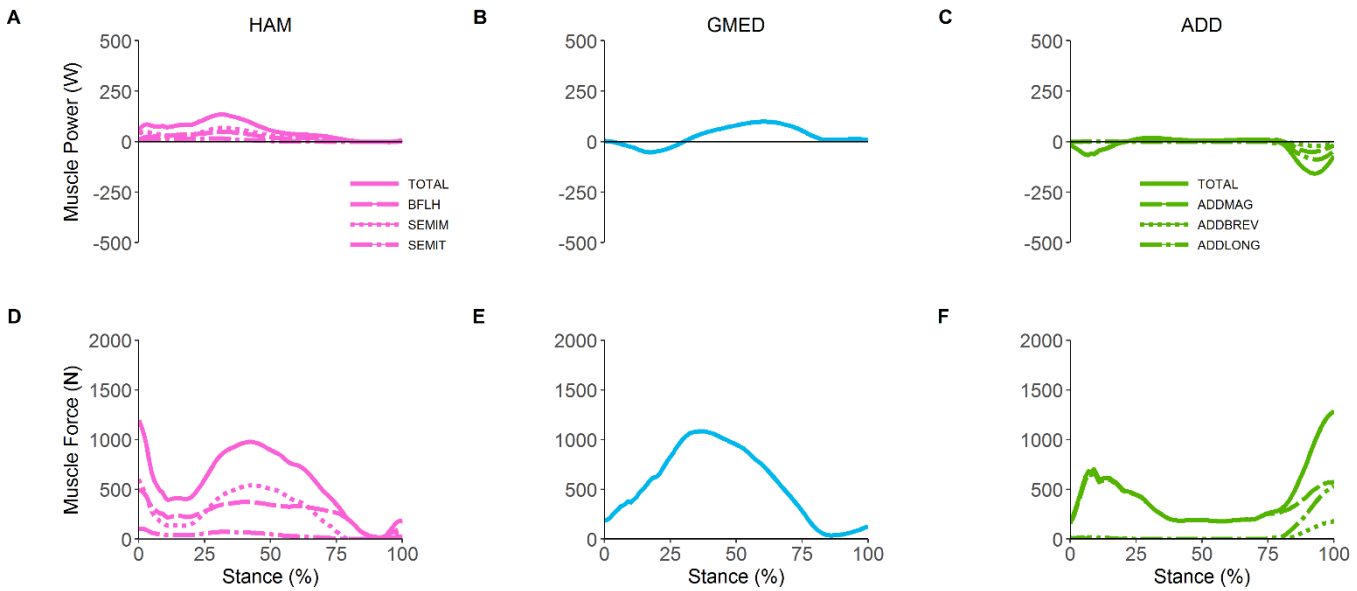
Appendix II Figure 3. Lower-limb joint moments computed via inverse dynamics (ID) and the residual reduction algorithm (RRA) during the stance phase of a 45º unanticipated sidestep cut.



Appendix II Figure 4. Summary of residual forces and moments after residual reduction algorithm during the stance phase of a 45° unanticipated sidestep cut. Panels, A, residual forces across the stance phase; B, residual moments across the stance phase; C, density distribution of root mean square errors for residual forces; D, density distribution of root mean square errors for residual moments; E, density distribution of maximum residual forces; F, density distribution of maximum residual moments.



Appendix II Figure 5. Musculotendinous powers (top row) and forces (bottom row) for muscles that were primary contributors to the ground reaction forces during the stance phase of a 45º unanticipated sidestep cut. VASTI, vasti (vastus intermedius, lateralis and medialis); VASINT, vastus intermedius; VASLAT, vastus lateralis; VASMED, vastus medialis; GAS, gastrocnemius; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; SOLEUS, soleus; GMAX, gluteus maximus.



Appendix II Figure 6. Musculotendinous powers (top row) and forces (bottom row) for muscles that were secondary contributors to the ground reaction forces during the stance phase of a 45° unanticipated sidestep cut. HAM, biarticular hamstrings; BFLH, biceps femoris long head; SEMIM, semimembranosus; SEMIT, semitendinosus; GMED, gluteus medius; ADD, adductors; ADDMAG, adductor magnus; ADDBREV, adductor brevis; ADDLONG, adductor longus. Note the smaller y-axis scale compared to Appendix II Figure 5.

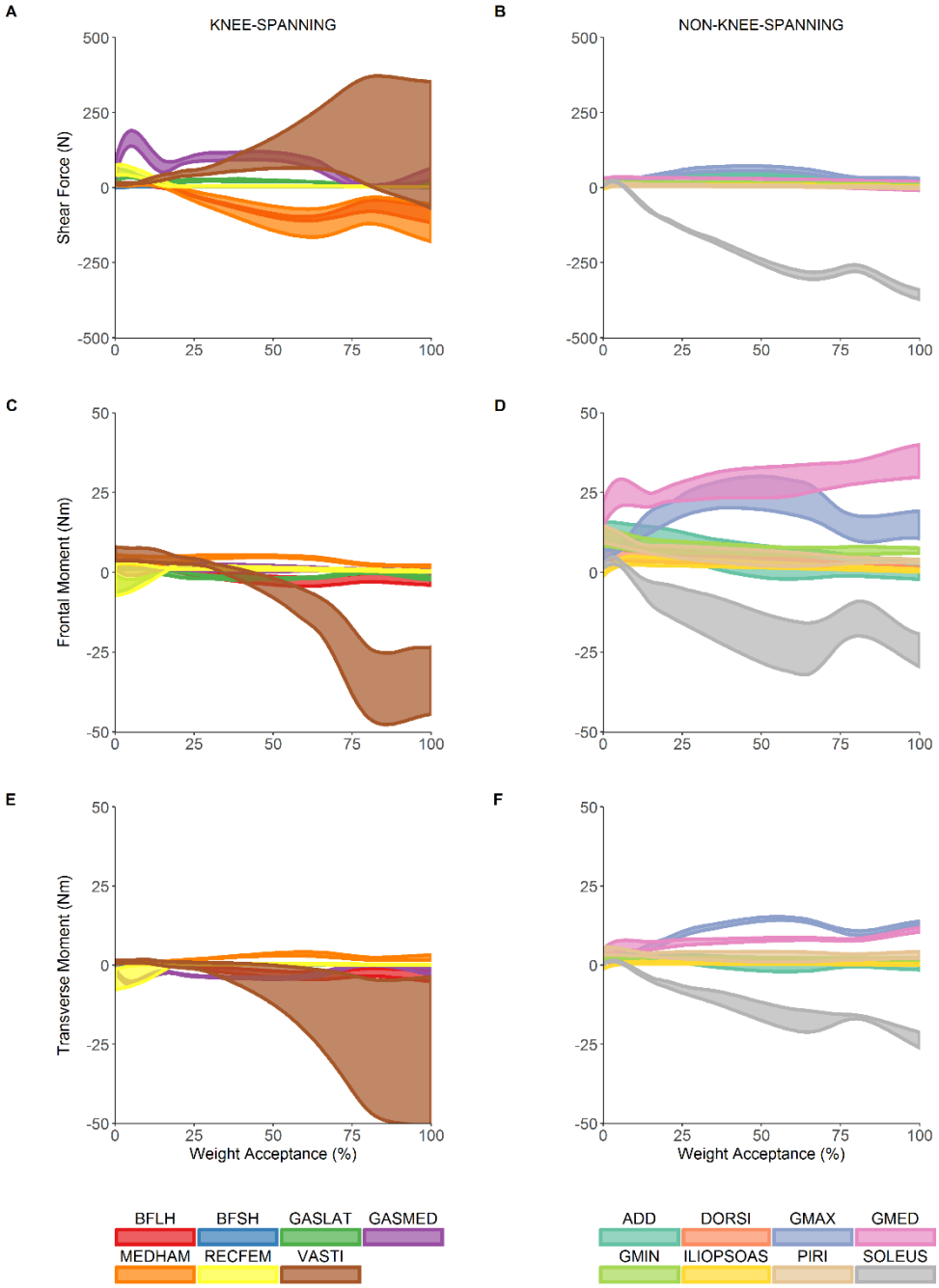
Appendix II Table 13. Root mean square and maximum errors between joint positions derived from inverse kinematics and the residual reduction algorithm.

Coordinate	Root mean square error (mean ± SD)	Maximum error (mean ± SD)
Pelvis translation (cm)		
tx	1.0 ± 0.6	1.7 ± 0.9
ty	2.4 ± 0.6	3.3 ± 0.8
tz	0.8 ± 0.5	1.2 ± 0.7
Pelvis rotation (º)		
Tilt	0.83 ± 0.48	1.45 ± 0.87
List	0.81 ± 0.42	1.69 ± 0.95
Rotation	0.91 ± 0.30	1.65 ± 0.50
Hip rotation (º)		
Flexion	0.64 ± 0.29	1.55 ± 0.65
Adduction	0.65 ± 0.19	1.30 ± 0.37
Rotation	0.44 ± 0.18	1.24 ± 0.51
Knee rotation (º)		
Flexion	0.74 ± 0.33	1.75 ± 0.74
Ankle rotation (º)		
Flexion	1.31 ± 0.14	2.86 ± 0.39

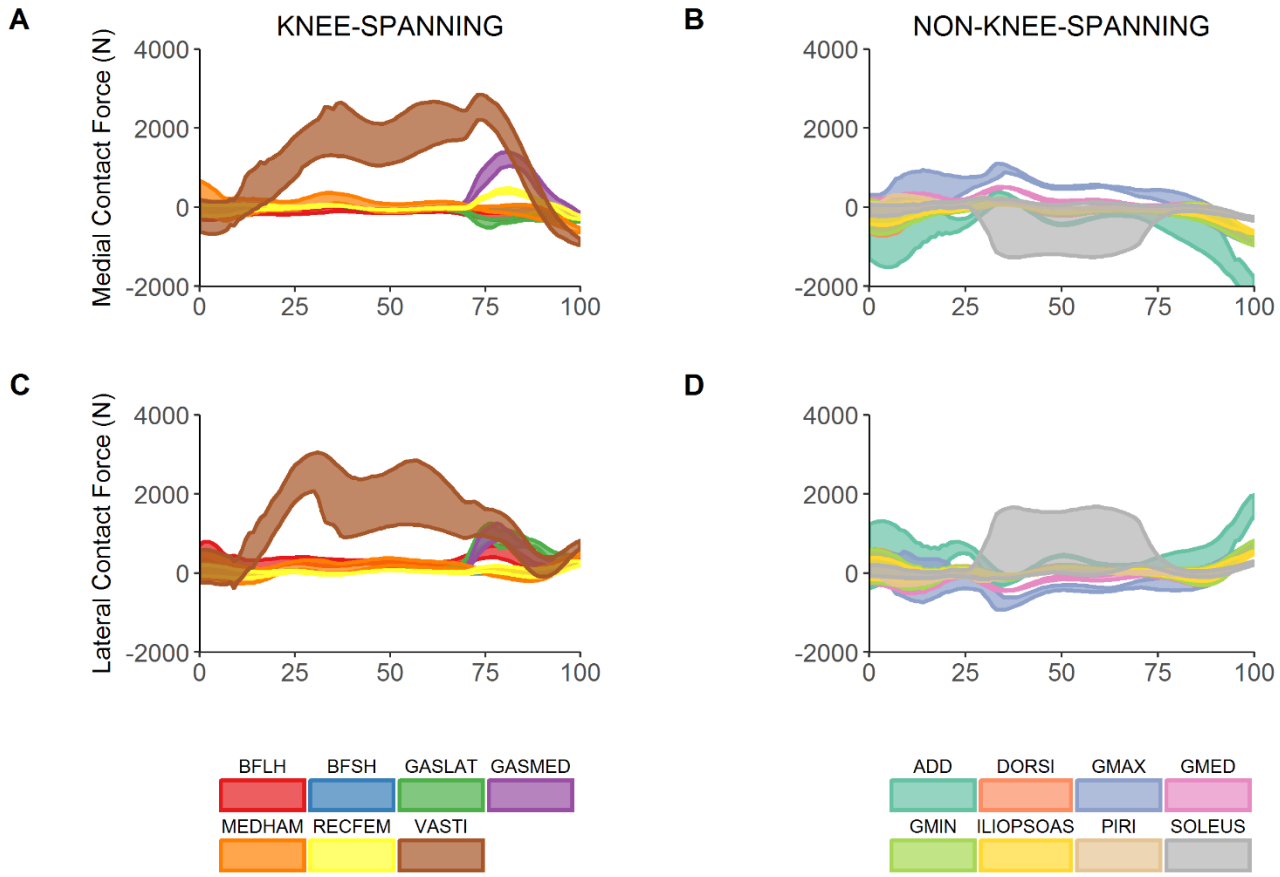
Note that the root mean square computations in this table were not normalised similar to other variables reported within the manuscript because currently recommended thresholds for the values reported in this table are typically reported in degrees and centimeters (e.g. (166)). tx, anteroposterior translation; ty, vertical translation; tz, mediolateral translation; SD, standard deviation.

Appendix III: Supplementary information related to post-hoc sensitivity analysis

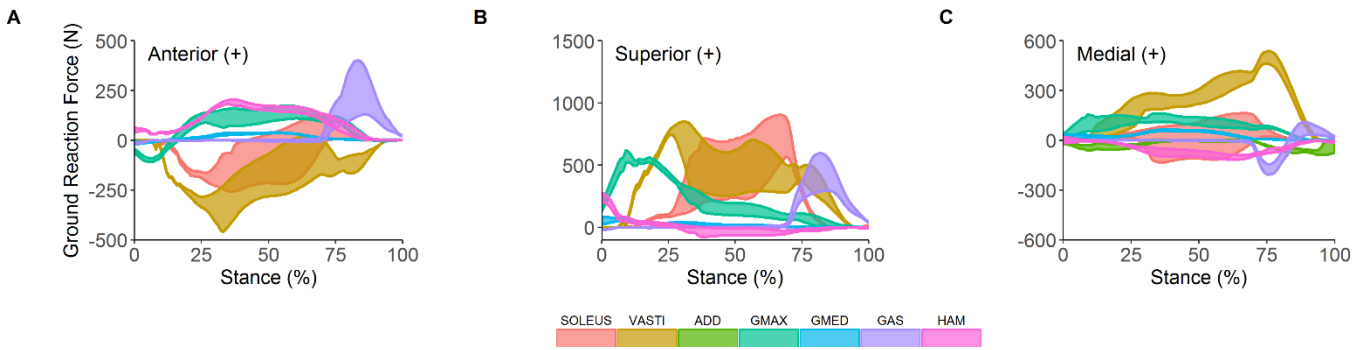
The following section contains supplementary material related to Chapter 8, which describes post-hoc sensitivity analysis to ensure the conclusions of Chapters 5, 6 and 7 were robust to key assumptions and uncertainties.



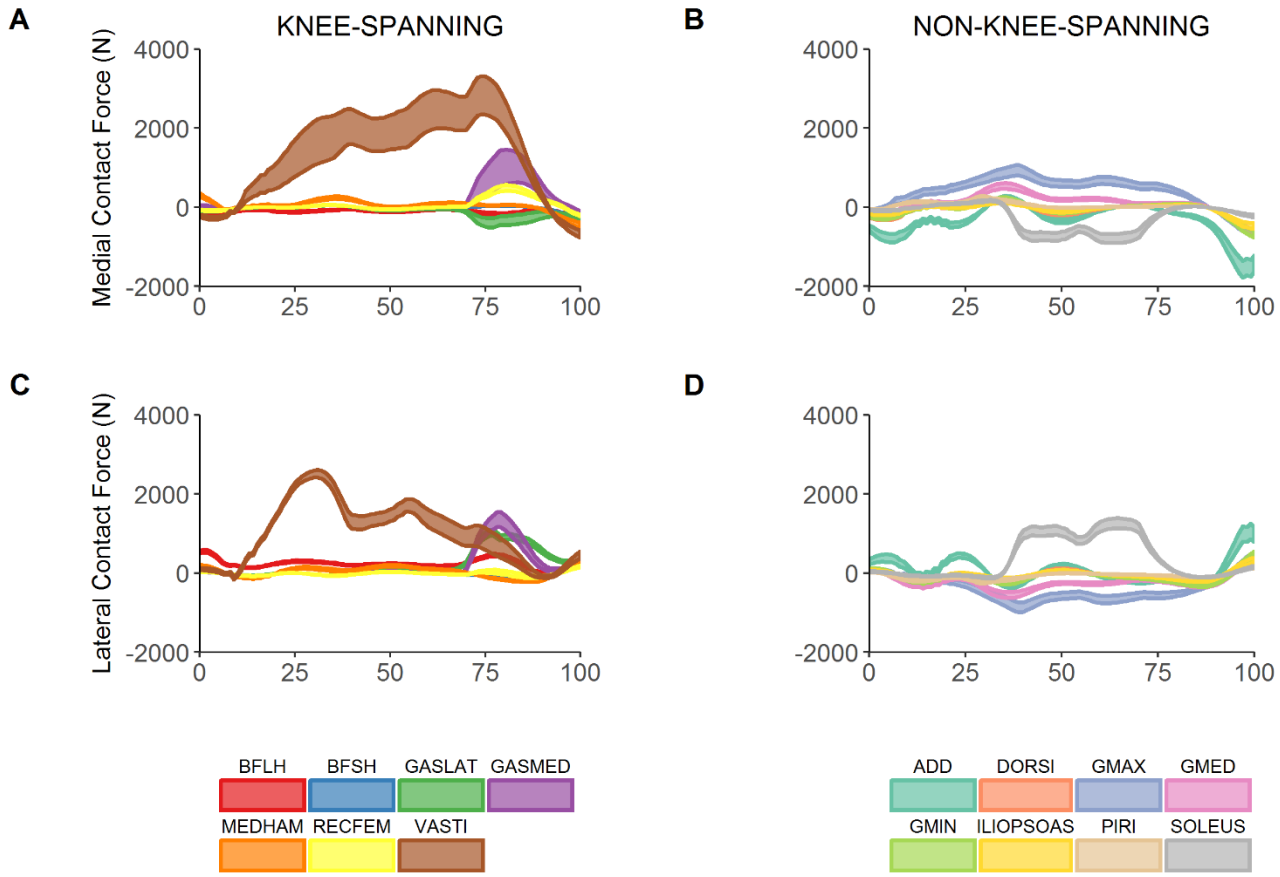
Appendix III Figure 1. Sensitivity of muscular contributions to knee anteroposterior shear joint reaction force (row 1), frontal plane knee joint reaction varus/valgus moment (row 2) and transverse plane knee joint reaction internal/external rotation moment (row 3) to 10º frontal and transverse plane tibiofemoral perturbations during the weight acceptance phase of the 45º unanticipated sidestep cut. Shaded regions represent the range of values produced by the four conditions (+10º valgus, varus, internal and external rotation). BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOLEUS, soleus.



Appendix III Figure 2. Sensitivity of muscular contributions to compressive forces in the medial (top row) and lateral (bottom row) tibiofemoral compartments to 10º frontal and transverse plane tibiofemoral perturbations during the stance phase of a 45º unanticipated sidestep cut. Shaded regions represent the range of values produced by the four conditions (+10º valgus, varus, internal and external rotation). BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOLEUS, soleus.



Appendix III Figure 3. Sensitivity of muscular contributions to ground reaction forces to 10º frontal and transverse plane tibiofemoral perturbations during the stance phase of the 45º unanticipated sidestep cut. Panel A, anteroposterior; B, superior-inferior; C, mediolateral. Shaded regions represent the range of values produced by the four conditions (+10º valgus, varus, internal and external rotation). SOLEUS, soleus; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); GMAX, gluteus maximus; GMED, gluteus medius; GAS, gastrocnemius (gastrocnemius medialis and lateralis); HAM, hamstrings (biceps femoris long head, semimembranosus and semitendinosus).



Appendix III Figure 4. Sensitivity of muscular contributions to compressive forces in the medial (top row) and lateral (bottom row) tibiofemoral compartments to 20% (~4mm) frontal plane perturbations of tibiofemoral contact points during the stance phase of a 45° unanticipated sidestep cut. Shaded regions represent the range of values produced by the four conditions (contact points move further apart, closer together, and both moved medially and laterally). BFLH, biceps femoris long head; BFSH, biceps femoris short head; GASLAT, gastrocnemius lateralis; GASMED, gastrocnemius medialis; MEDHAM, medial hamstrings (semitendinosus and semimembranosus); RECFEM, rectus femoris; VASTI, vasti (vastus intermedius, lateralis and medialis); ADD, adductors (adductor brevis, longus and magnus); DORSI, dorsi-flexors (tibialis anterior, extensor digitorum and hallucis longus), GMAX, gluteus maximus; GMED, gluteus medius; GMIN, gluteus minimus; ILIOPSOAS, iliopsoas (iliacus and psoas major); PIRI, piriformis; SOLEUS, soleus.

Appendix IV: Ethics approval information

The following section contains material related to ethics approval relating to the work conducted in Chapters 5, 6 and 7. Note that the ACU Human Ethics Committee Approval Number is 2015-11H.

PARTICIPANT INFORMATION LETTER

PROJECT TITLE: The influence of hamstring function on knee joint function in male and female athletes
PRINCIPAL INVESTIGATOR: Dr David Opar
STUDENT RESEARCHER: Mr Nirav Maniar
STUDENT'S DEGREE: Doctor of Philosophy

Dear Participant,

You are invited to participate in the research project described below.

What is the project about?
The research project investigates the impact of biomechanical factors and varying levels of hamstring function on the loading of the anterior cruciate ligament (ACL) in the knee. It is already known that a previous injury to the ACL in the knee joint increase the risk of sustaining a hamstring injury in the future. But what is not known is if a previous hamstring strain injury (HSI) might increase the risk of ACL injury. The hamstrings play an important role in protecting the ACL from damage/injury, however injury to the hamstrings reduces their ability to function properly. This study will examine how varying levels of hamstring function (structure, strength and flexibility) affect ACL loading during change of direction and a drop jump task.

The research team requests your assistance because you are aged 15-40 years old and are currently competing in a sport, at a recreational level or higher, that is known for its relatively high risk of HSI or ACL injury. Furthermore, you have either have a history of HSI on one limb only (with no history of ACL or any other recent lower limb injury), ACL injury in one limb only (with no history of hamstring or any other recent lower limb injury), or no prior HSI or ACL injury.

Who is undertaking the project?
This project will be conducted by Mr Nirav Maniar and will form the basis for the degree of Doctor of Philosophy at Australian Catholic University under the supervision of Dr David Opar.

Are there any risks associated with participating in this project?
The research team does not anticipate any major risks. The anticipated/unanticipated change of direction and drop jump task may carry a small risk of injury or reinjury. However, these tasks will be performed in a controlled laboratory setting, and subsequently pose less risk than your usual sport/training. Furthermore, these tasks have been performed in numerous other studies, none of which have reported any injuries. Both the student researcher and primary investigator have experience with these testing procedures, and at least one will be present to ensure that you employ safe and correct techniques at all times. In the unlikely event that injury does occur, we will apply standard first aid treatment (ice, elevation and compression). If the injury impedes your ability to transport yourself home safely, alternative transportation arrangements will be organised by the investigators, at no cost to you. We will also be able to provide you with advice and assistance regarding your rehabilitation; however we are not able to provide you with primary care (i.e. physiotherapy). In order to ensure your safety, it is important you inform the investigator of any

unusual sensations or pain you experience during any tests, no matter how minor. This will ensure that the investigator can immediately terminate the test.

What will I be asked to do?

Participation in this project will require one-two 120-180 minute testing sessions, separated by at least 24 hours.

During these sessions, we will conduct assessments of your hamstring function. In the first session, you will first have your hamstring muscle architecture (involving factors which detail how your muscle is built) assessed. This will be undertaken utilising two-dimensional ultrasound in a rested and sub-maximally contracted state. This assessment will require you to lie face down on a custom made device with the back of your thigh surface exposed. A site of interest, approximately 50% of the distance between your ischial tuberosity (pelvis) and your knee fold, will be determined for each leg. Once this site has been determined, you will be asked to relax and the assessment will be undertaken. Following this assessment you will then be instructed to perform a sub-maximal contraction at a predetermined force. During this contraction, you will be instructed to maintain the contraction at this force whilst your muscle architecture is assessed. This will be completed with both legs. Hamstring length (or flexibility) will be assessed by four basic tests. In two of these instances, you will be required lay flat on your back, with your hip flexed (pull thigh towards your torso) at 90 degrees, whilst your knee is relaxed. In one assessment, the researcher will straighten your knee whilst you remain fully relaxed. Once a certain degree of resistance is felt, the knee angle will be measured. The other test is identical, except you will actively straighten your knee by contracting your quadriceps (thigh) muscles (no assistance will be provided by the researcher), with the knee angle measured when you are unable to straighten your knee any further. Similarly, the other two tests also require that lay flat on your back, except this time your knee will remain straight as your leg is raised. One test will require that you lift your leg, whilst the other test will involve the investigator lifting your leg for you. Your hip angle will be measured when you feel you are unable to lift or have your leg lifted any further without bending your knee. You will be asked to do multiple strength assessments. In the first, you will be positioned lying on your back, with the hips and knees flexed to 90° with both heels resting on a firm plinth. After placing the cuff of a digital sphygmomanometer (blood pressure cuff) under your heel, you will be asked to push your heel into the cuff as hard as possible by flexing the knee (i.e. pulling back). The next test will involve you lying on your back, with one heel (test leg) on a 60cm box. The test leg is slightly bent at the knee, whilst the non-test leg is held in a vertical position. You then raise your bottom off the ground by pushing down through the heel, with the aim of the test being to do as many repetitions as possible. The third strength assessment will have you positioned on your knees (on a padded board) with your ankles secured via ankle braces. From here, you will slowly lower yourself to the ground by allowing your knees to straighten. This lowering movement will be controlled by contracting your hamstrings forcefully, until you eventually catch yourself at the bottom with your hands.

In the second visit, you will be fitted with small recording electrodes over your hamstring, quadriceps and calf muscles on both of your legs. The final strength assessment requires that you are seated in a machine called a dynamometer. The heel of your test leg is placed in contact with a lever that can measure your force output. After an appropriate warm-up, you will then be asked to exert as much force as you can as rapidly as possible can against the load cell by contracting your hamstrings. The measurement device will not move, so you will be exerting against an immovable object. After these, you will complete a few more contractions, except this time the lever will move through a range of motion (from the knee straight to the knee bent at 90 degrees) at a controlled speed. The final tasks are a 3D biomechanical assessment. In these tasks, you will be fitted with reflective markers at various positions over your body (primarily at your joints), as these allow us to analyse your joint angles and

forces. You will then be asked to perform several tasks, the first being normal walking at a self-selected speed. Next, we will ask you to perform an anticipated cutting manoeuvre, where you will run a short distance to a target point, and rapidly change to a predetermined direction. The second task is the same, except you will not know which way you need to change direction until you reach the change of direction point. The direction you need to change will be communicated to you only once you have reached the target point. The third task is a single leg hop for distance, in which you will begin on one leg, then hop for a predetermined distance and land on the same leg from which you jump off. You will then be asked to perform two hops in a row, with each hop being the same predetermined distance as in the previous task. The next task is the drop jump, in which you will begin on a small box (no more than 50% of your standing height) and will then drop off followed by an immediate and maximal vertical jump. Finally, you will be asked to do a single leg landing after a drop of a box of no more than 50% of your standing height. Note that you will be given the opportunity to complete a familiarisation prior to the actual task during the testing session, meaning that you will perform all three of these tasks (but we won't collect any data from this familiarisation).

How much time will the project take?

Participation will involve one to two sessions of 120-180 min at the School of Exercise Science at the Australian Catholic University (Melbourne Campus).

What are the benefits of the research project?

It is not expected that this project will benefit you in the short term. In the long term, if prior HSI or other hamstring function tests are found to have an impact on the ability of the hamstring muscles to protect the ACL this could have significant implications for the prevention of ACL injuries in the future.

Can I withdraw from the study?

Participation in this study is completely voluntary. You are not under any obligation to participate. If you agree to participate, you can withdraw from the study at any time without adverse consequences. Your decision to participate will in no way impact upon your current or future relationship with ACU (for example your grades) or with any of the investigators. If you do choose to withdraw from participation, the data collected up until that point may still be used by the investigators for the research purposes stated, unless otherwise requested by you. Should you choose to request that your data not be used, you will face no adverse consequences.

Will anyone else know the results of the project?

It is intended that the results of this research will be submitted for publication within scholarly journals. All test results, comments and responses are anonymous and will be treated confidentially.
All data obtained:

- Will be stored for at least 5 years by the research team.
- Will not be used for any other purpose (e.g. as an instructional aide).
- Can be accessed only by the research team.

Will I be able to find out the results of the project?

All results will be available to be communicated to the participants upon their request for the data once their involvement within the program is complete. Participants are encouraged to contact the investigators once this occurs. No distribution of data to the participants will occur without this prior request. Upon the request for the data, the participants will be given an individualised letter, outlining the specific information obtained. Participants will also be informed of any publication from the study (pending its acceptance).

Who do I contact if I have questions about the project?

Mr Nirav Maniar
Phone: 0415 515 668
Email: Nirav.Maniar@acu.edu.au

Dr David Opar
Phone: 61 3 9953 3742
Email: david.opar@acu.edu.au

What if I have a complaint or any concerns?

This research has been reviewed by the Human Research Ethics Committee at Australian Catholic University (review number 201500011H). If you have any complaints or concerns about the conduct of the project, you may write to the Chair of the Human Research Ethics Committee care of the Office of the Deputy Vice Chancellor (Research).

Manager, Ethics
c/o Office of the Deputy Vice Chancellor (Research)
Australian Catholic University
North Sydney Campus
PO Box 968
North Sydney, NSW, 2059
Ph: 02 9739 2519
Fax: 02 9739 2870
Email: res.ethics@acu.edu.au

Any complaint or concern will be treated in confidence and fully investigated. You will be informed of the outcome.

I want to participate! How do I sign up?

Please contact Mr Nirav Maniar or Dr David Opar to have any questions answered or if you require further information about the project.
If you would like to participate we would like to ask you to sign a written consent form (enclosed) to confirm your agreement to participate.

Yours sincerely,
Mr Nirav Maniar
Dr David Opar

PARTICIPANT CONSENT FORM

Copy for Researcher / Copy for Participant to Keep

TITLE OF PROJECT: The influence of hamstring function on knee joint function in male and female athletes

(NAME OF) PRINCIPAL INVESTIGATOR (or SUPERVISOR): Dr David Opar

(NAME OF) STUDENT RESEARCHER: Mr Nirav Maniar

I ..... *(the participant)* have read (*or, where appropriate, have had read to me)* and understood the information provided in the Letter to Participants. Any questions I have asked have been answered to my satisfaction.

I agree to participate in this study encompassing one-two (2) 120-180 minute visits, realising that I can withdraw my consent at any time if I feel any discomfort or for any other reason (without adverse consequences). I understand that these visits will involve the assessment of hamstring muscle architecture, flexibility and strength, and the performance of a drop jump and change of direction task as outlined in the information letter. I agree that research data collected for the study may be published or may be provided to other researchers in a form that does not identify me in any way.

Note that if you are under the age of 18, you and your parent/guardian are also required to read and sign the guardian consent form.

NAME OF PARTICIPANT: .....

SIGNATURE ..... DATE .....

SIGNATURE OF PRINCIPAL INVESTIGATOR (or SUPERVISOR): .....

DATE:.....

SIGNATURE OF STUDENT INVESTIGATOR: .....

DATE:.....

GUARDIAN CONSENT FORM

Copy for Researcher / Copy for Parent/Guardian to Keep

TITLE OF PROJECT: The influence of hamstring function on knee joint function in male and female athletes

(NAME OF) PRINCIPAL INVESTIGATOR (or SUPERVISOR): Dr David Opar

(NAME OF) STUDENT RESEARCHER: Mr Nirav Maniar

I ..... *(the parent or guardian)* have read (*or, where appropriate, have had read to me)* and understood the information provided in the Letter to Participants. Any questions I have asked have been answered to my satisfaction.

I agree for …….. *(the participant)* to participate in this study encompassing one-two (2) 120-180 minute visits, realising that they can withdraw consent at any time if they feel any discomfort or for any other reason (without adverse consequences). I understand that these visits will involve the assessment of hamstring muscle architecture, flexibility and strength, and the performance of a drop jump and change of direction task as outlined in the information letter. I agree that research data collected for the study may be published or may be provided to other researchers in a form that does not identify the participant in any way.

NAME OF PARTICIPANT: ……

SIGNATURE ..... DATE

.....

NAME OF GUARDIAN: ……

SIGNATURE ..... DATE .....

SIGNATURE OF PRINCIPAL INVESTIGATOR (or SUPERVISOR): .....

DATE:……..

SIGNATURE OF STUDENT INVESTIGATOR: .....

DATE:……..

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