

THE INFLUENCE OF MOVEMENT PROFILE ON THE FEMALE ATHLETE'S
BIOMECHANICAL RESILIENCE & TRAINING LOAD RESPONSE TO CONTROLLED
EXERCISE EXPOSURE

Barnett S. Frank

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Approved by:

Darin A. Padua

Anthony C. Hackney

Steven W. Marshall

Claudio L. Battaglini

J. Troy Blackburn

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ABSTRACT

Barnett S. Frank: The Influence Of Movement Profile On The Female Athlete's Biomechanical Resilience & Training Load Response To Controlled Exercise Exposure
(Under the Direction of Darin A. Padua)

Background: “Stiff” landing biomechanics and excessive frontal plane knee motion, such as limited trunk, hip, and knee flexion and medial knee displacement have been identified as risk factors or movement patterns associated with lower extremity musculoskeletal injury and elevated joint loads. Additionally, high training load exposure has similarly be linked to musculoskeletal injury in the physically active population. There is a significant volume of evidence supporting high training loads and high-load biomechanics to independently influence injury risk. However there is a lack evidence describing the influence of an individual's baseline movement quality profile on their systemic and musculoskeletal tissue stress experienced secondary to high training load exposure. An individual's global resilience to high training loads may be influenced by the mechanical demands of their inherent movement profile during physical activity and sport participation.

Aim: Investigate the influence of an individual's inherent baseline movement profile on their biomechanical, systemic stress, and musculoskeletal system stress response to an acute bout of high training load exposure.

Methods: 43 physically active, healthy, college-aged females were enrolled in this study and were assigned to a *poor* high-load or *excellent* low-load movement profile group operationally defined by the Landing Error Scoring System (LESS). Jump-landing 3D

biomechanics and blood samples were collected prior to and following a metabolically controlled acute high training load exercise protocol (HTL). Changes in biomechanics and circulating biomarkers of global systemic stress (cortisol), and musculoskeletal system tissue stress (sCOMP & CK-MM) were compared between *poor* and *excellent* movement profiles to better understand the influence of movement profile on the body's response to the demands of HTL.

Results: The *poor* group was observed to experience greater degradation of neuromuscular control strategies that effectively and efficiently dissipate mechanical stresses experienced during high-intensity exercise. Furthermore, we observed movement profile to influence systemic stress hormone levels (cortisol). A *poor* movement profile was associated with an elevated stress level in contrast to their *excellent* movement counterparts. Furthermore, it seems the *excellent* movement profile is linked to greater deployment of dynamic muscle tissue to efficiently dissipate the high mechanical stresses experienced during HTL activities, as the *excellent* movement profile was associated with greater circulation of CK-MM following acute HTL exposure.

Conclusions: Movement quality profile influences the physically active, healthy, college-aged female's biomechanical and global stress response to HTLs associated with sport participation. The *excellent* movement quality profile appears to be more biomechanically resilient to acute HTL exposure. Thus, promoting an *excellent* movement profile in individuals partaking in exercise activity with HTLs is encouraged to limit global stress levels, and promote safe neuromuscular control strategies limiting the mechanical load exposure to the system.

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LIST OF ABBREVIATIONS & SYMBOLS

ACL: Anterior Cruciate Ligament

C1,2C: Carboxy-Terminus of 3/4 Peptide From Cleavage of Type-I & Type-II Collagen

C2C: Neoepitope From Cleavage Of Type-II Collagen

CK: Creatine Kinase

COMP: Cartilage Oligomeric Matrix Protein

CPII: Type-II Procollagen Carboxy-Propeptide

CTx-II: C-Telopeptide Of Type-II Collagen

ELISA: Enzyme Linked Immuosorbent Assay

HIE: High-Intensity Exercise

HTL: High Training Load

IL-6: Interleukin-6

LESS: Landing Error Scoring System

MKD: Medial Knee Displacement

MSK: Musculoskeletal

OA: Osteoarthritis

RPE: Rating of Perceived Exertion

sCOMP: Serum Cartilage Oligomeric Matrix Protein

sCORT: Serum Cortisol

SOVO_{2submax}: Speed-Only Graded Submaximal Aerobic Capacity Assessment

VeT: Ventilatory Threshold

VO_{2max}: Maximal Aerobic Capacity

CHAPTER 1

INTRODUCTION

Musculoskeletal (MSK) injuries during sport and physical activity are common (Conn, Annett, and Gilchrist 2003), costly (Woolf and Pfleger 2003; Jacobs 2008), and have long-term health consequences (Lohmander et al. 2007; Maffulli et al. 2010), representing a substantial socioeconomic burden (Cumps et al. 2008; Shephard 2003). Injury severity is the primary determinant of an injury's cost to society (van Mechelen 1997; van Mechelen, Hlobil, and Kemper 1992). Individuals who sustain a high-severity sport-related MSK injury such as an anterior cruciate ligament (ACL) rupture experience sizeable direct and indirect medical costs, acute and long-term decreases in productivity that result in a reduction in human capital, and decreases in quality of life (van Mechelen 1997; van Mechelen, Hlobil, and Kemper 1992; Cumps et al. 2008). Thus, there is a considerable need to understand underlying factors that may contribute to an increased risk of experiencing a high-severity MSK during sport and physical activity to reduce the socioeconomic burden of MSK injury while maximizing the health benefits of sport and physical activity participation.

The current body of literature has identified lower extremity biomechanics to be both risk factors (2006; Dallinga, Benjaminse, and Lemmink 2012; Shultz et al. 2012) and mechanisms (Krosshaug et al. 2007; Shimokochi and Shultz 2008) for sport-related ACL injury. Thus biomechanics are associated with an individual's prospective risk for sport-related ACL injury, and are readily identifiable during injury events.

Interestingly, over 50% to 70% of sport-related ACL injuries are reported to be the result of a noncontact mechanism of injury (Agel, Arendt, and Bershadsky 2005; Boden et al. 2000; Mihata, Beutler, and Boden 2006; Mountcastle et al. 2007). Noncontact mechanisms causing sport-related ACL rupture are described as “forces applied to the knee at the time of injury that result from an athlete’s own movement that did not involve contact with another athlete or object” (Marshall, Padua, and McGrath, n.d.). Thus, an athlete’s self-imposed motion is responsible for injury.

Recent studies suggest that high training load (HTL) exposure similar to the physical demands of sport participation elicits changes in lower extremity biomechanics associated with noncontact ACL injury (Quammen et al. 2012; Santamaria and Webster 2010; Webster et al. 2012; SCHMITZ et al. 2014). Current evidence links fatigue (Galambos et al. 2005) and high training loads (Gabbett 2004; Gabbett and Jenkins 2011) to increased injury rates. Furthermore, the physiological effects of sport participation can result in high levels of markers of total body / systemic stress (Rietjens et al. 2005; Thorpe and Sunderland 2012), muscle damage (Rietjens et al. 2005; Thorpe and Sunderland 2012), and joint loading (Andriacchi et al. 2004; Dominguese and Seegmiller 2012; Santamaria and Webster 2010) that may explain an individual’s predisposition to injury.

Individuals with *poor* lower extremity biomechanics may experience an exacerbated adaptation in biomechanics linked to noncontact ACL injury after exposure to HTL demands experienced during sport. Specifically, individuals with *poor* biomechanics may exhibit greater non-sagittal plane loading at the knee and hip after HTL exposure, such as greater frontal and transverse plane energy absorption (Santamaria and Webster 2010), imparting high shearing stresses on lower extremity articular joint surfaces associated with articular cartilage degradation

(Andriacchi et al. 2004). Furthermore, when individuals adopt non-sagittal plane energy absorption strategies they may recruit frontal and transverse plane dynamic stabilizing musculature to maintain safe hip and knee joint control, reducing energy absorption efficiency, resulting in a potentially higher total body physiological demand. Therefore, the volume of total body stress, muscle damage, and joint stress experienced by those with *poor* biomechanics may be greater after HTL exposure. However, the influence of *poor* biomechanics on total body stress, muscle damage, and joint load during HTL exposure is currently unknown. Developing an understanding of the influence of *poor* lower extremity biomechanics on systemic stress and MSK system tissue damage is important, because poor biomechanics are modifiable, and can be improved during sport and physical activity participation (Distefano et al. 2010; Distefano et al. 2011; Padua et al. 2011; Dempsey et al. 2009). Therefore, clinicians may be able to decrease systemic and MSK tissue stress during HTL scenarios by means of improving biomechanics through corrective exercise interventions, reducing an individual's susceptibility to injury during sport or physical activity participation.

Clinical movement screenings such as The Landing Error Scoring System (LESS) can validly and reliably discriminate between individuals with *poor* and *excellent* movement profiles (APPENDIX 1) (Padua et al. 2009). Biomechanics associated with a *poor* movement profile and the readily identifiable medial knee displacement (MKD) movement pattern are linked to numerous lower extremity injuries, including ACL injury (Shultz et al. 2010), patellofemoral pain syndrome (Mizuno et al. 2001; Elias et al. 2004), medial collateral ligament injury (Hull et al. 1996), lower-leg stress fracture (Cameron, Peck, and Owens 2014), as well as the progression of knee osteoarthritis (OA) (Sharma et al. 2001; Brouwer et al. 2007). Mounting evidence suggests that corrective exercise programming and lower extremity injury prevention programs

can significantly improve lower extremity biomechanics to limit MKD and other non-sagittal plane loading patterns that characterize a *poor* movement profile during functional tasks (Bell et al. 2013; Zebis et al. 2008; Barendrecht et al. 2011); improving lower extremity neuromuscular control and subsequent movement efficiency during athletic participation. Although corrective exercise and lower extremity injury prevention programs are consistently reported to effectively reduce knee injury incidence during sport participation (Sadoghi, Keudell, and Vavken 2012; Taylor et al. 2013), the underlying mechanisms responsible for injury risk reduction remain elusive.

The influence of an individual's movement profile on their mechanical tissue loading and physiological response to sport and physical activity participation is not currently described. Previous research has focused on the influence of lower extremity neuromuscular control on future risk of lower extremity injury. Abnormal knee and hip biomechanics such as increased knee abduction moment (Farrokhi et al. 2013; 2002; 2013) and hip internal rotation (2007) are associated with increased joint loading at the tibiofemoral and patellofemoral joint in pathological populations (Farrokhi et al. 2013). However, the combined influence of an individual's pre-existing / baseline movement profile and HTL exposure on MSK tissue loading and systemic physiological stress has not been evaluated.

An individual with pre-existing deficits in lower extremity neuromuscular control may experience higher mechanical tissue loading and greater subsequent physiological stress during athletic participation compared to an individual with an ideal movement profile (figure 1.1). Indirect evaluation of joint loading can be accessed via circulating biochemical markers of articular cartilage metabolism and evaluation of cartilage thickness via radiograph (Boockock et al. 2009; Niehoff et al. 2011) or ultrasonography (Naredo et al. 2009), while markers of the

systemic physiological response to exercise manifest in circulating markers of total body hormonal stress response, muscle tissue damage, and subjective perceived exertion (Knicker et al. 2011; Purvis, Gonsalves, and Deuster 2010; Thorpe and Sunderland 2012). Individuals with deficits in lower extremity neuromuscular control such as a *poor* movement profile and MKD may experience greater tissue loading and total body stress responses driving a potential increased risk for injury when exposed to a HTL. Furthermore, individuals with deficits in lower extremity neuromuscular control may present with elevated markers of tissue loading and total body physiological stress prior to HTL exposure due to chronic abnormal soft tissue demands and joint loading. Identifying a link between a movement profile representative of *poor* lower extremity neuromuscular control and joint and physiological stress may further explain an individual's heightened risk of lower extremity injury during athletic participation. Combining the influence of biomechanical lower extremity risk factors for injury and physiological markers of systemic stress and exercise-induced MSK tissue damage may provide clinicians with an improved capacity to identify athletes at high risk for injury, and facilitate development of more effective intervention methods aimed at reducing an individual's vulnerability for injury during sport participation.

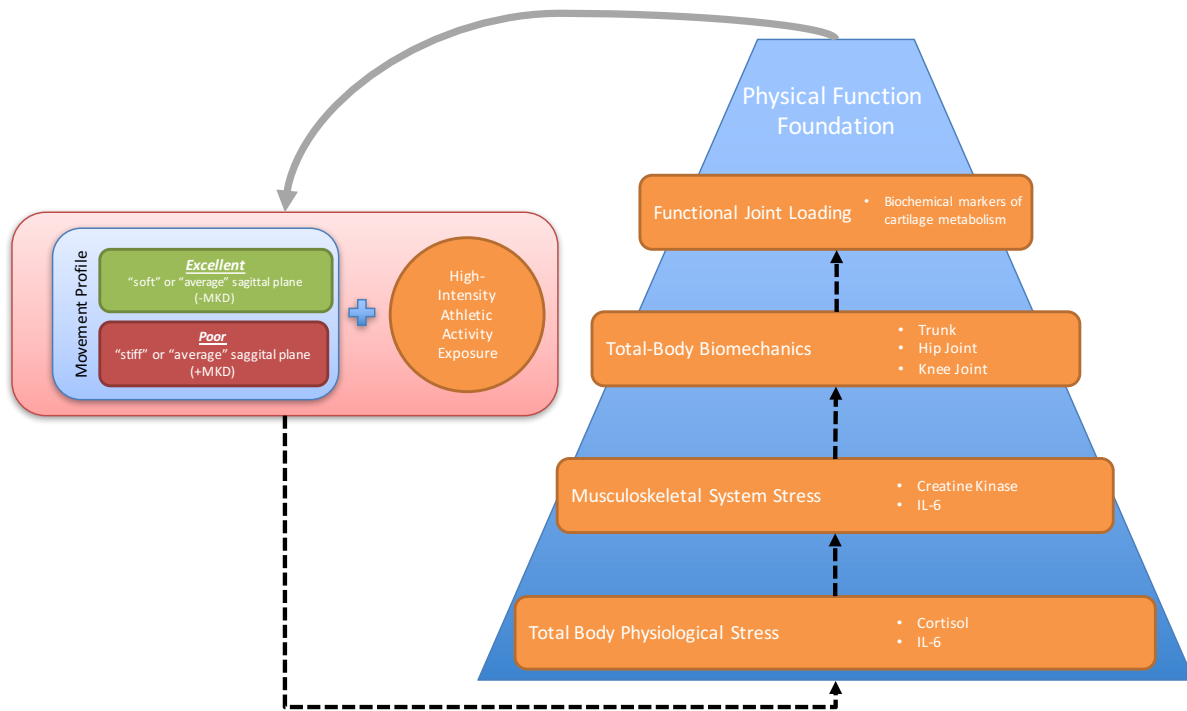


Figure 1.1 - Conceptual model depicting the potential influence of and individual's baseline movement profile on their systemic and musculoskeletal system tissue stress in response to high-intensity exercise exposure.

Currently, the strongest link between training stress and MSK injury is a subjective measure of training load; calculated by multiplying an athlete's session rate of perceived exertion (RPE) by the duration of the activity (Gabbett and Jenkins 2011). Exposure to higher training loads has been linked to increases in the hormone cortisol, an endocrine system marker of systemic stress (Gomes et al. 2013). Similarly, elevated levels of creatine kinase (CK), a marker of skeletal muscle damage has been observed during periods of higher intensity training or competition in athletes (Coutts et al. 2007; Uchida et al. 2009). Evidence implicates subjective assessment of training load to be a sufficient measure of objectively assessed markers of systemic physiological and MSK system tissue stress imposed on the body during sport participation, as elevated levels of cortisol and CK are both linked to higher levels of training stress (Gomes et al. 2013; Thorpe and Sunderland 2012; Coutts et al. 2007). To date there is a

lack of information regarding the underlying physiological link between increased training load and injury risk.

A majority of research has focused on the effects of lower extremity corrective exercise / injury prevention programs on biomechanics and injury rates in the active population, however there is a lack of understanding regarding how an individual's movement profile affects the athlete's systemic stress response, consequent changes in biomechanics associated with injury, and MSK system tissue damage. An investigation regarding the effects of aberrant lower extremity biomechanics on consequential physiological stress markers and biological markers of MSK system tissue damage and metabolism is warranted (figure 1.2). The overall aim of this study was to evaluate the effect of an individual's baseline movement profile on MSK system tissue damage, systemic stress and biomechanical response to HTL exposure simulating the physical demands of field and court sport. A total of 43 female court and field and court sport athletes with *poor* (n= 21) and *excellent* (n= 22) movement profiles was recruited for participation in this study to better understand the impact of an individual's movement profile on MSK system tissue damage and systemic stress response to HTL.

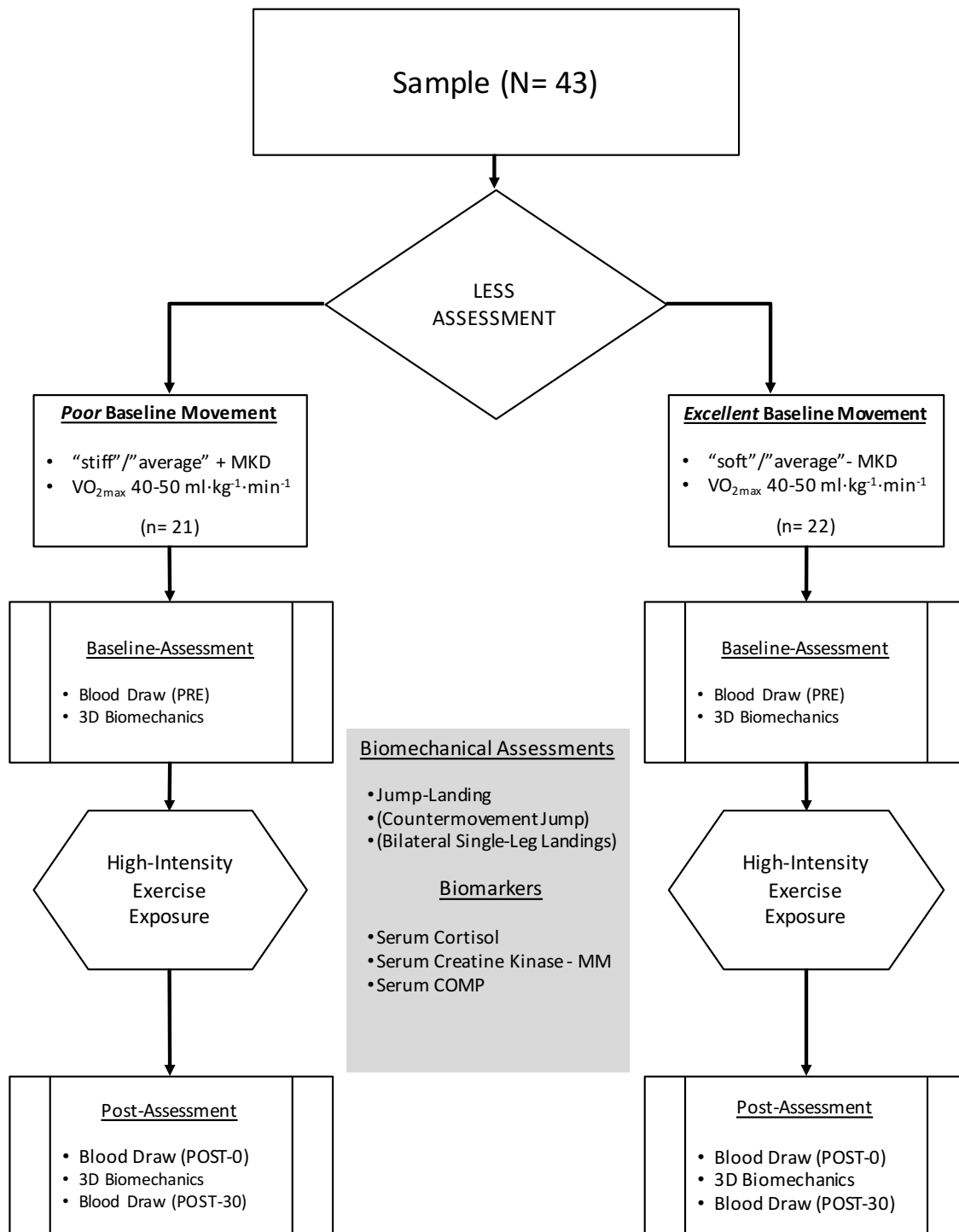


Figure 1.2 – Overview of the P study methodology to evaluate the effects of an individual’s baseline movement profile on their musculoskeletal tissue damage and systemic stress response to high-intensity exercise exposure.

Operational Definitions

1. *High Training Load (HTL) Protocol*: An exercise protocol lasting approximately 28 minutes comprised of 6 sets of a 5-minute interval of treadmill running at a speed coincident with 115 – 120% of a participant's ventilatory threshold (VeT) and 10 repetition jump-landing interval. This protocol has been identified to induce elevations in measures of systemic stress and global fatigue responses associated with the high physical demands of field and court sport participation.
2. *Poor Baseline Movement Profile*: An “average” or “stiff” landing characterized as “very little, if any trunk, hip, and knee displacement.” with medial knee displacement (APPENDIX 1).
3. *Excellent Baseline Movement Profile*: An “average” or “soft” landing characterized as “large displacement of the trunk, hips, and knees” with medial knee displacement (APPENDIX 1).
4. *Medial Knee Displacement (MKD)*: Visually observed frontal plane medial displacement of the center of the patella relative to the first ray during the loading phase of a jump-landing.
5. *Submaximal Aerobic Capacity (VO_{2max})*: The maximal volume of oxygen (ml) consumed per unit (kg) body mass per unit time (minute) measured via ventilatory gas exchange during a *speed only* graded exercise test ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$).
6. *Ventilatory Threshold (VeT)*: Quantified using the V-slope method (Albouaini et al. 2007), an exercise intensity (treadmill speed) representative of the point at which pulmonary minute ventilation increases disproportionately to oxygen consumption during the *speed only* graded exercise test.

7. *Serum Cartilage Oligomeric Matrix Protein (sCOMP) Concentration*: Venous blood sample serum concentration ($\text{ng} \cdot \text{dl}^{-1}$) assessed using an enzyme-linked immunosorbent assay (ELISA) reflective of cartilage matrix disruption / degradation.
8. *Serum Cortisol Concentration*: Venous blood sample serum concentration ($\text{ng} \cdot \text{dl}^{-1}$) assessed using an ELISA reflective of systemic stress level.
9. *Serum Creatine Kinase MM-Isoform (CK-MM) Concentration*: Venous blood sample serum concentration ($\text{ng} \cdot \text{dl}^{-1}$) assessed using an ELISA representative of exercise-induced muscle damage.
10. *Jump-Landing Task*: A functional movement task imposing physical demands similar to landing from a jump during sport activity as in “rebounding” during basketball. Participants jump down from a 30 cm high “jump box” to a target line placed $\frac{1}{2}$ the participant’s height anterior to the “jump box” and immediately jumping upward for maximal height.
11. *Sagittal Plane Knee Angle*: Local coordinate system angulation of the shank segment rigid body relative to the thigh segment rigid body about the knee joint’s medio-lateral axis ((+) Flexion / (-) Extension).
12. *Frontal Plane Knee Angle*: Global coordinate system angulation of the shank segment rigid body and the thigh segment rigid body axes ((+) Varus / (-) Valgus).
13. *Sagittal Plane Knee Moment*: Net internal soft-tissue force acting about the knee joint’s medio-lateral axis formed by the moment arms of shank segment and thigh segment rigid bodies ((+) Flexion / (-) Extension).

14. *Frontal Plane Knee Moment*: Net internal soft-tissue force acting about the knee joint's anterior-posterior axis formed by the moment arms of shank segment and thigh segment rigid bodies ((+) Varus / (-) Valgus).
15. *Proximal Anterior Tibial Shear Force*: The net linear force applied in the anterior direction at the tibiofemoral joint causing anterior translation of the shank rigid body in the reference frame of the x -axis of the femur translated to the distal end of the femur rigid body.
16. *Sagittal Plane Hip Angle*: Local coordinate system angulation of the thigh segment rigid body relative to the pelvis segment rigid body about the hip joint's medio-lateral axis ((+) Flexion / (-) Extension).
17. *Frontal Plane Hip Angle*: Local coordinate system angulation of the thigh segment rigid body relative to the pelvis segment rigid body about the hip joint's antero-posterior axis ((+) Adduction / (-) Abduction).
18. *Sagittal Plane Hip Moment*: Net internal soft-tissue force acting about the hip joint's medio-lateral axis formed by the moment arms of thigh segment and pelvis segment rigid bodies ((+) Flexion / (-) Extension).
19. *Frontal Plane Hip Moment*: Net internal soft-tissue force acting about the hip joint's antero-posterior axis formed by the moment arms of thigh segment and pelvis segment rigid bodies ((+) Adduction / (-) Abduction).
20. *Sagittal Plane Trunk Angle*: Local coordinate system angulation of the thorax segment rigid body relative to the pelvis segment rigid body about the L5-S1 joint interspace's medio-lateral axis ((+) Flexion / (-) Extension).

21. *Frontal Plane Trunk Angle*: Local coordinate system angulation of the thorax segment rigid body relative to the pelvis segment rigid body about the L5-S1 joint interspace's anterior-posterior axis ((+) Rightward / (-) Leftward).
22. *Vertical Ground Reaction Force*: The vertical components of the ground reaction force vectors of the right and left force platforms equal in magnitude and opposite in direction to the force imparted by participants when they are in contact with the ground atop the right and left force platforms normalized to the participant's mass.
23. *Initial Ground Contact*: The first time point during each jump-landing trial when the right or left force platform registers a vertical ground reaction force >10N.
24. *Toe-Off*: The first time point during each jump-landing trial when the right or left force platform registers a vertical ground reaction force <10N after initial ground contact.
25. *Stance Phase*: The period of time between initial ground contact and toe-off, representing the period of time in which the participant's right or left foot is in contact with the right or left force platform during the jump-landing task.
26. *Biomechanical Response Change Score and Confidence Interval Waveforms*: All biomechanical data will be analyzed as continuous normalized waveforms during the stance phase of the jump-landing (Kuenze et al. 2014). Interpolated kinematic and kinetic data will be normalized to 201 data points (knots) over the stance phases of the middle 3 jump-landing task trials using a cubic spline function. Each knot will be calculated as the mean value of the respective derived knots from each of the 3 middle jump-landing tasks (eq. 1) (trial 2, trial 3, trial 4).

$$Knot_{i...201} = \frac{Knot_{i\ t2} + Knot_{i\ t3} + Knot_{i\ t4}}{3}$$

(eq. 1)

To calculate changes in biomechanical variables from baseline to post-exercise, the difference between the respective individual baseline and post-HIE knot values ($knot_{bi}$ & $knot_{fi}$) was calculated to form a 201 knot waveform reflecting the change in the biomechanical variable of interest (eq. 2).

$$Knot_{\Delta i \dots 201} = Knot_{fi} - Knot_{bi}$$

(eq. 2)

Average change score ensemble means and 95% confidence interval waveforms will be calculated for sagittal and frontal plane trunk, hip, and knee joint angles. Change score waveforms will be calculated for sagittal and frontal plane internal net hip and knee joint moments. Furthermore, change score waveforms will also be calculated for proximal anterior tibial shear force and vertical ground reaction force variables.

LIMITATIONS & ASSUMPTIONS

1. Biomechanical calculations from the motion analysis system and biomechanical software are reliable and valid.
2. The principal investigator is an “expert” LESS rater, and thus accurately and reliably is able to identify *poor* and *excellent* baseline movement profiles of study candidates.
3. The HIE protocol represents a generalizable simulation of the physical demands of field and court sports.
4. Participants honestly report their rate of perceived exertion during the VeT assessment and the HTL exercise exposure.
5. Participants jump for maximal vertical height during the jump-landing tasks during the HIE protocol and biomechanical assessment.

6. The ELISA kits are reliable within <10% inter and intra-assay coefficients of variation.
7. Circulating serum concentrations of sCOMP accurately and reliably reflect articular cartilage metabolism.
8. Circulating serum concentration of cortisol accurately and reliably reflects systemic stress level.
9. Circulating serum CK-MM accurately and reliably reflects levels of exercise-induced skeletal muscle damage.
10. The MSK system tissue damage, systemic stress, and biomechanical responses of college-aged club field and court sport athletes to HTL is generalizable to the high-risk female athlete population at high-risk for sport-related noncontact ACL injury.

DELIMITATIONS

1. 43 female participants (21 *poor* & 22 *excellent*) will be recruited from the local university population.
2. All participants were between the ages of 18 – 24 years of age.
3. All participants were healthy with no history of upper or lower extremity joint surgery, spine surgery, or neurological or metabolic disorders.
4. All participants were injury-free at the time of testing, and had no history of lower or upper extremity MSK injury that limited their participation from sport or exercise for more than 3 days.
5. All participants had previous history of competitively participating in a field or court sport (soccer, lacrosse, basketball, rugby, team handball, field hockey, volleyball, tennis) for at least one year of varsity level participation during high-school.

6. All participants had an estimated maximal aerobic capacity between
40 – 50 ml•kg⁻¹•min¹.
7. Participants demonstrate MKD and an “average” or “stiff” landing OR participants
demonstrate a “soft” or “average” landing without MKD.
8. Segment kinematic data was collected from the trunk, thigh, shank, and foot using a 10-
camera optoelectric motion capture system.
9. Bilateral ground reaction force data was collected using two conductive in-ground
mounted force platforms.
10. All serum biomarker concentrations were measured using ELISA and spectrophotometry.

INDEPENDENT VARIABLE

1. Baseline movement profile
 - a. *Excellent vs. Poor*

DEPENDENT VARIABLES

1. Baseline and Post-HIE Exposure Serum Biomarker Concentrations:
 - a. sCOMP
 - b. Cortisol
 - c. CK-MM
2. Change Score and 95% Confidence Interval Ensemble Waveforms for the Following
Biomechanical Variables Normalized to 202 Data Points Over The Stance Phase of the
Jump-Landing Task:
 - a. Sagittal plane knee joint angle

- b. Frontal plane knee thigh-shank segment angle
- c. Sagittal plane hip joint angle
- d. Frontal plane hip joint angle
- e. Sagittal plane trunk angle
- f. Frontal plane trunk angle
- g. Net internal sagittal plane knee joint moment
- h. Net internal frontal plane knee joint moment
- i. Net internal sagittal plane hip joint moment
- j. Net internal frontal plane hip joint moment
- k. Proximal anterior tibial shear force
- l. Vertical ground reaction force

RESEARCH QUESTIONS

1. What are the effects of an individual's baseline movement profile on changes in circulating biomarkers of MSK system tissue damage and mechanical stress in response to HTL?
 - a. Compare the magnitude and direction of changes from pre to post-HTL in serum sCOMP concentration between participants with *poor* and *excellent* baseline movement profiles.
 - b. Compare the magnitude and direction of changes from pre to post-HTL in serum CK-MM concentration between participants with *poor* and *excellent* baseline movement profiles.

2. What are the effects of an individual's baseline movement profile on changes in circulating biomarkers of systemic stress and peripheral fatigue in response to HIE?
 - a. Compare the magnitude and direction of changes from pre to post-HIE in serum cortisol concentration between participants with *poor* and *excellent* baseline movement profiles.
3. What are the effects of an individual's baseline movement profile on changes in biomechanics associated with sport-related noncontact ACL injury in response to HIE?
 - a. Compare the ensemble change scores and associated 95% confidence interval waveforms for sagittal and frontal plane trunk, hip, and knee kinematics during the stance phase of the jump-landing task between individuals with *poor* and *excellent* baseline movement profiles.
 - b. Compare the ensemble change scores and associated 95 confidence interval waveforms for sagittal and frontal plane hip and knee moments during the stance phase of the jump-landing task between individuals with *poor* and *excellent* baseline movement profiles.
 - c. Compare the ensemble change score and associated 95confidence interval waveforms for proximal anterior tibial shear force during the stance phase of the jump-landing task between individuals with *poor* and *excellent* baseline movement profiles.
 - d. Compare the ensemble change score and associated 95% confidence interval waveforms for the vertical ground reaction force during the stance phase of the jump-landing task between individuals with *poor* and *excellent* baseline movement profiles.

HYPOTHESES

1. Individuals with *poor* and *excellent* baseline movement profiles will experience different magnitudes of MSK system tissue stress in response to HTL exposure such that:
 - a. The *poor* group will experience greater elevations in markers of cartilage degradation, with the *poor* group experiencing greater elevations in sCOMP relative to baseline following HTL exposure compared to the *excellent* group.
 - b. The *poor* group will exhibit greater elevations in exercise-induced muscle damage, with the *poor* group experiencing greater elevations in CK-MM relative to baseline following HTL exposure compared to the *excellent* group.
2. Individuals with *poor* and *excellent* baseline movement profiles will experience greater magnitudes of systemic stress in response to HTL exposure characterized by:
 - a. The *poor* group will experience greater elevations in serum cortisol compared to the *excellent* group.
3. Individuals with *poor* baseline movement profiles will exhibit a greater tendency and magnitude in changes toward biomechanics associated with sport-related noncontact ACL injury in response to HTL exposure compared to individuals with *excellent* baseline movement profiles such that:
 - a. The *poor* group will exhibit greater decreases in sagittal plane hip and knee motion with concomitant increases in frontal plane hip and knee motion toward hip adduction and knee valgus or varus motion over the stance phase of the jump-landing task compared to the *excellent* group. Furthermore, the *poor* group will

demonstrate greater changes toward forward and lateral trunk flexion motion compared to the *excellent* group during the stance phase of the jump-landing task.

- b. The *poor* group will exhibit greater decreases in sagittal plane hip extension moment with concomitant increases in sagittal plane knee extension moment compared to the *excellent* group. Additionally, the *poor* group will exhibit greater increases in internal hip adduction and knee varus moment during the stance phase of the jump-landing task compared to the *excellent* group.
- c. The *poor* group will experience greater increases in proximal anterior tibial shear force during the stance phase of the jump-landing compared to the *excellent* group.
- d. The *poor* group will experience greater increases in vertical ground reaction force during the stance phase of the jump-landing compared to the *excellent* group.

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CHAPTER 2

Physical Activity Participation Must be Promoted to Improve Population Health

Non-communicable disease represents 65% of all-cause mortality and 44% of premature deaths per year (World Health Organization, 2010). Physical inactivity was responsible for 9% of the world's premature mortality in 2008, and has been linked to the leading causes of death classified as non-communicable diseases (Lee et al. 2012). Physical inactivity is directly attributable to 6% of coronary heart disease, 7% of type II diabetes, and 10% of colon and breast cancer (Lee et al. 2012). Non-communicable disease represents a significant socioeconomic burden on the world's population (Pratt et al. 2014), thus interventions and behaviors that limit the prevalence of non-communicable disease should be promoted (Hallal et al. 2012; Garber et al. 2011). Regular exercise participation significantly reduces an individual's risk of non-communicable disease (Garber et al. 2011; Lee et al. 2012). High-level evidence implicates exercise significantly reduces an individual's risk of developing coronary heart disease, breast and colon cancer, and type II diabetes by 20-40% (United States Department of Health & Human Services, 2008, (Burns and Murray 2014). Physical activity participation is perhaps the single-most effective health behavior to reduce non-communicable disease risk (Lee et al. 2012). Thus improving and maintaining physical activity participation in the population is a significant priority to improve world health.

Although engagement in physical activity has been reported to promote health benefits, participation in sport and fitness activity is not without potential adverse consequence. Physical

activity participation has an overall unintentional injury incidence of 25.9 injuries per 1,000 persons, with musculoskeletal injury amassing to over 50% of all injuries sustained (Conn, Annest, and Gilchrist 2003). Two hundred and seventeen million Americans engaged in regular physical activity in 2012, representing 76% of the United States population aged six years or greater (Council 2012). Considering the unintentional injury incidence associated with physical activity, the total number of musculoskeletal injuries associated with physical activity is large and may create a significant burden on the healthcare system.

Musculoskeletal (MSK) injury represents an economic burden surmounting to 9% of The United States gross domestic product (Jacobs 2008). Thus, as a population we are presented with a dilemma; physical inactivity has adverse health consequences (Lee et al. 2012; Trost, Blair, and Khan 2014) but participation in sport increases one's risk for sustaining MSK injury (Conn, Annest, and Gilchrist 2003). Understanding the epidemiology of sport and physical activity related injury helps to direct interventions aimed at reducing an active individual's risk for sustaining MSK injury during sport and physical activity participation. Enabling safe sport and physical activity participation permits the population to participate in an effective protective health behavior while reducing the negative consequences of sustaining a MSK injury.

SECTION ONE: Epidemiology of Sport-Related Musculoskeletal Injury

Lower Extremity Musculoskeletal Injury in Sport & Physical Activity

MSK injury accounts for 53.5% (3.75 million injuries) of the population estimated 7 million sport and physical activity related injuries that occur each year in the United States (Conn, Annest, and Gilchrist 2003). Sport-related MSK injury occur at an incidence of almost 26 injuries per 1,000 population individuals (Conn, Annest, and Gilchrist 2003). Sprain and strain

injuries (31.5%) represent a majority of injury diagnoses compared to other MSK conditions, rivaled only by the frequency of fractures (22%) (Conn, Annest, and Gilchrist 2003). Extremity injuries account for over 70% of the sprains and strains sustained by athletes and the physically active population (Conn, Annest, and Gilchrist 2003). While upper extremity injuries are common in sport and physical activity participation, lower extremity MSK diagnoses consistently amount to a majority of reported sport-related injuries in multiple populations, ranging from the recreationally active (Conn, Annest, and Gilchrist 2003) through youth (Clausen et al. 2014; Conn, Annest, and Gilchrist 2003; Fernandez, Yard, and Comstock 2007; Ruedl et al. 2012), collegiate (Hootman, Dick, and Agel 2007), and professional athlete populations (Walden, Hägglund, and Ekstrand 2005; Hägglund et al. 2013).

Specifically, knee and lower-leg conditions represent a majority of the sport-related injuries across all levels of athletic participation (Fernandez, Yard, and Comstock 2007; Hootman, Dick, and Agel 2007; Cumps et al. 2008; Hägglund, Waldén, and Ekstrand 2005; Walden, Hägglund, and Ekstrand 2005). In a secondary analysis of the High School Sport-Related Injury Surveillance System Study data, Fernandez et al. observed ankle (40.3%) and knee (25.3%) injuries to account for the majority of all sport-related injuries, of which 50% of injuries were diagnosed as ligamentous injury (Fernandez, Yard, and Comstock 2007). While it is clear ankle injuries occur with a higher frequency compared to knee injuries, the most common cause for surgery is knee injury for both male and female high school athletes (Fernandez, Yard, and Comstock 2007). Severe sport-related injuries resulting in surgery are associated with a significant unfavorable socioeconomic impact (Cumps et al. 2008; Gottlob et al. 1999; Gianotti, Hume, and Tunstall 2010; Marshall 2003).

Similar trends in MSK injuries requiring surgical intervention are observed at the extreme levels of sport participation. Amateur youth (Stracciolini et al. 2014; Gottschalk and Andrish 2011; D. Caine, Purcell, and Maffulli 2014) and elite professional (Waldén et al. 2011; Hägglund, Waldén, and Ekstrand 2005; Walden, Hägglund, and Ekstrand 2005; Hawkins and Fuller 1999) athletes have high incidences of knee injury requiring surgery. Furthermore, lower extremity MSK injury is a significant burden within the military (Hauret et al. 2010), a population exposed to high-intensity physical training and combat activity comparable to the physical demands of sport (Teyhen et al. 2014). A study by Hauret et al. in 2010 concluded that lower extremity injury accounted for 39% of all MSK injuries in the military, with injuries to the knee and lower-leg representing 22.4% of all injuries; more than double all upper extremity injuries combined (14.1% of total injuries) (Hauret et al. 2010). It is clear lower extremity MSK injury, specifically injuries to the knee, lower leg, and ankle occur at substantially higher rates compared to MSK injuries at other body locations in the physically active population. While MSK injuries to the lower-leg and ankle commonly have a higher incidence than knee injury, knee injury is responsible for a majority of surgeries associated with sport-related injury, contributing to a significant socioeconomic cost that reflects the surging burden of severe MSK injury and disease in the current population (Jacobs 2008; van Mechelen 1997; Turkiewicz et al. 2014).

Sport-Related Knee Injury is a Severe Injury

When setting targets for interventions aimed at preventing sport-related injury van Mechelen recommends first identifying the *extent of the problem* as a measure of the *cost* of the injury to society which is directly proportional to the incidence and severity of the injury (van Mechelen 1997). Tolpin et al. describes three primary socioeconomic costs of sport-related

injury; *Direct Costs*, *Indirect Costs*, and *Social Costs* (van Mechelen 1997; H. G. Tolpin, Vinger, and Tolpin 1981). *Direct Costs* represent the costs of medical treatment such as diagnostic expenses, physician / clinician and admissions fees, pharmacological treatments, material products (i.e. orthopaedic braces, orthotics, home-care equipment, & assistive mobility devices), and assistive labor (H. G. Tolpin, Vinger, and Tolpin 1981; van Mechelen 1997). *Indirect Costs* are expenditures incurred due to elevated levels of morbidity that are linked to disability, preventing individuals from executing their professional or career objectives effectively and efficiently, thus decreasing an individual's level of productivity, resulting in lost or decreased income and a depreciated human capital for society (Cumps et al. 2008; H. G. Tolpin, Vinger, and Tolpin 1981; van Mechelen 1997; Knowles et al. 2007). *Social Costs* are implicated to be less quantifiable compared to direct and indirect costs that are based on quantifiable monetary and time-loss measures. However, *Social Costs* represent the impact of injury on an individual's quality of life, ranging from indices that aim to assess levels of physical function, pain, general physical health, and mental health (H. G. Tolpin, Vinger, and Tolpin 1981; van Mechelen 1997). Together, the above costs represent the socioeconomic burden of an injury that affects both the injury victim and society as a whole, driving a flux in resource demand from the healthcare system on the broader economy in order to effectively manage and treat a sport-related injury acutely and over time.

The overall cost of a injury is most influenced by injury severity, determined by the nature of the sport-related injury, duration and nature of treatment, sporting time lost, working time lost, and permanent damage due to injury (van Mechelen 1997; Finch 1997). The knee joint is the most common site of severe sport-related injury within the athletic population (Darrow et al. 2009; Straccolini et al. 2014; Hootman, Dick, and Agel 2007; Walden, Hagglund, and

Ekstrand 2005). The knee has been observed to account for over 81% of complete ligament sprains in athletes (Darrow et al. 2009). Complete ligamentous ruptures commonly require high-cost surgical intervention for treatment and long-duration rehabilitation (greater than 6 months), thus resulting in substantial time loss from sport and working time loss, further contributing to the higher severity of knee injury compared to other sport-related MSK conditions (D. Caine, Purcell, and Maffulli 2014; de Loës, Dahlstedt, and Thomée 2000; Cumps et al. 2008).

The direct link between high-severity sport-related knee injury and high-cost surgical intervention is evident. Knee injury represents 53.9% of all severe injuries requiring surgery in the high school athlete population, with 41.9% of all diagnoses requiring surgery involving ligament sprains (Darrow et al. 2009). Furthermore, in a study of Swiss youth athletes, severe knee injuries account for only 10% and 13% of all sport-related injuries in males and females. Yet, sport-related knee injury contributes to the highest cost-per-hour injury in sport participation, amounting to 27% and 33% of total sport-related injury expenditures (de Loës, Dahlstedt, and Thomée 2000). In a Flemish population-based study, non-specific knee injury (including meniscal and articular cartilage involvement) was second only to anterior cruciate ligament (ACL) injury direct costs (Cumps et al. 2008). ACL injury direct costs more than double the direct medical costs of any other costly sport-related injuries (Cumps et al. 2008).

Anterior Cruciate Ligament Injury is Responsible for High-Severity Knee Injury

The body of sport injury epidemiology research recognizes the knee to be the most common body location to sustain a severe injury during sport participation spanning all levels of sport competition (Conn, Annest, and Gilchrist 2003; Darrow et al. 2009; Gottschalk and Andrish 2011; Walden, Hagglund, and Ekstrand 2005; Hootman, Dick, and Agel 2007). ACL injury represents a knee injury diagnosis with perhaps the highest-level of severity as defined by

van Mechelen and Tolpin et al. As a diagnosis involving rupture of one of the primary passive stabilizers of the knee joint, the *nature* of the injury implicates a relatively complex surgical repair with a high *direct cost* (\$11,500 (Gottlob et al. 1999) – \$12,713 (Mather et al. 2013) per reconstruction) in attempt to restore physiological function of the joint.

ACL injuries also carry a high *indirect cost* as a result of decreased human capital. A single anterior cruciate ligament reconstruction (ACLR) represents a \$38,121 mean lifetime cost to society, while conservative management of a ACL rupture has been reported to surmount to \$88,538 mean lifetime cost to society (Mather et al. 2013). A long-duration recovery to pre-injury physical functioning following a ACL rupture results in longer sport time and work time lost compared to other MSK conditions such as less a severe ligamentous injury to the ankle (Hagglund, Walden, and Ekstrand 2006; Walden, Hagglund, and Ekstrand 2005; Conn, Annest, and Gilchrist 2003; Fernandez, Yard, and Comstock 2007).

Intra-articular knee joint injury such as ACL rupture and meniscal tears are linked to subsequent decreased physical function after injury (Lentz et al. 2012; Lohmander et al. 2004; Lohmander et al. 2007; Oiestad et al. 2010), increased risk of osteoarthritis (OA) (Lohmander et al. 2004; Lohmander et al. 2007; Oiestad et al. 2010; Friel and Chu 2013; Lentz et al. 2012), and increased knee pain (Lohmander et al. 2004; Lohmander et al. 2007; Oiestad et al. 2010; Lentz et al. 2012). There is a clear negative impact of ACL injury on quality of life, a measure of *social cost*. Additionally, quality of life may be diminished further, as the time from injury onset increases due to the increased risk for development of post-traumatic knee OA, suggesting ACL injury results in *permanent damage*. The high direct, indirect, and social costs of ACL injury in the athletic and physically active population identify ACL injury as a MSK condition responsible for a substantial negative socioeconomic impact. van Mechelen's priority for identifying sport-

related injuries implicates sport-related ACL injury should be a target for preventative interventions within the population (van Mechelen 1997).

The Landscape of ACL Injury in Sport

In order to have the largest public health impact, an intervention must target both a population and context that contributes to the highest socioeconomic burden regarding a health condition, disease, or injury condition (Fixsen et al. 2005; Hanson et al. 2014). Identifying populations with high incidence of ACL injury will help aim interventions to promote a public health impact. ACL injury incidence has been studied on a basis of sport participation, sex, age, previous injury history, and level of participation. While sport-related ACL injury is not 100% avoidable, previous findings implicate more than 50% to 70% of ACL injuries are a result of a noncontact mechanism (Agel, Arendt, and Bershadsky 2005; Boden et al. 2000; Mihata, Beutler, and Boden 2006; Mountcastle et al. 2007). A noncontact mechanism is described as “forces applied to the knee at the time of injury that result from an athlete’s own movement that did not involve contact with another athlete or object.” (Marshall, Padua, and McGrath, n.d.) Thus, an athlete’s self-imposed motion is responsible for injury, suggesting improvement of an athlete’s control of his or her own motion can decrease likelihood of ACL injury.

Understanding factors that contribute to an increased risk of noncontact ACL injury is important. Clinicians can effectively prevent up to 85% of ACL injuries through training programs aimed to improve neuromuscular control during athletic activity (Sadoghi, Keudell, and Vavken 2012). While controlled neuromuscular training programs have proved efficacious, recent evidence suggests ACL injury rates are rising in the athlete population (Mall et al. 2014; Hootman, Dick, and Agel 2007). Understanding the combined influence of population and contextual factors that are associated with a high incidence of ACL injury is imperative in order

to more effectively decrease the burden of ACL injury on society. The remainder of this literature review aims to identify a target population at high risk for ACL injury that results in substantial socioeconomic impact. Furthermore, this review will identify a potential context for heightened ACL injury risk, proposing the interaction between the high-risk population and a high-load training environment that may further explain underlying mechanisms of ACL injury.

The Influence of Sport Participation on ACL Injury Incidence – Targeting High-Risk Sports

Sport participation is associated with a majority of ACL injuries in the population (Gianotti, Hume, and Tunstall 2010; Mall et al. 2014). While sport participation alone is a significant predisposing factor for sustaining an ACL injury, injury incidence varies between different sports. Large epidemiological studies commonly report that all competition levels of soccer to carry a high ACL injury incidence, even when adjusting for the influence of sex and age (Agel, Arendt, and Bershadsky 2005; Hootman, Dick, and Agel 2007; Waldén et al. 2011; Dick et al. 2007; Joseph et al. 2013). Male high school soccer athletes have an ACL injury incidence of 4.8 per 100,000 practice or competition events, with females having an incidence of 12.2 ACL injuries per 100,000 practice or competition events (Joseph et al. 2013). Collegiate-level soccer injury rates range from 0.12 in males to 0.33 injuries per 1,000 athlete exposures (defined as one player participating in a practice or competition) in females (Agel, Arendt, and Bershadsky 2005). Professional male soccer athletes have an ACL injury incidence between 0.035 – 0.039 per 1,000 player-hours, while female's have an ACL injury incidence of 0.057 (Waldén et al. 2011). Comparatively, sports such as high-school baseball and volleyball have relatively low ACL injury incidences at 0.7 and 2.4 injuries per 100,000 practice or competition events (Joseph et al. 2013). A significant limitation to the current body of sport-epidemiology research is the lack of consistency in incidence estimations, using various calculations of the

denominator of athlete exposure. Common practices are to report athlete exposures as athletes per unit time (i.e. player-hours) or per unit of training or competition session (i.e. team practice or match play). While there is considerable inconsistency in incidence calculations, it is clear that sports involving rapid changes in direction and landing from a jump exhibit the highest incidences of ACL injury (Boden et al. 2000; Myklebust et al. 1998; Myklebust, Skjølberg, and Bahr 2013; Olsen et al. 2004).

Epidemiological evidence of high rates of ACL injury in sports requiring rapid changes in direction and landing is further supported by comprehensive National Collegiate Athletic Association (NCAA) injury surveillance system (ISS) data which identifies women's gymnastics (0.33 per 1,000 player-competitions or practices), soccer (0.32), basketball (0.29), and lacrosse (0.18), and men's football (0.14) to carry the highest incidences of ACL injury compared to other NCAA sports (Arendt, Agel, and Dick 1999; Agel, Arendt, and Bershadsky 2005; Hootman, Dick, and Agel 2007). Two additional sports that carry a significant risk for ACL injury that involve similar rapid changes in direction are rugby (Prodromos et al. 2007; Mountcastle et al. 2007) and team handball (Myklebust, Skjølberg, and Bahr 2013; Moses, Orchard, and Orchard 2012). Female team handball presents with an incidence of 0.31 ACL injuries per 1,000 player-hours (Myklebust et al. 1998) with an overall injury rate of 0.48 injuries per team per season collapsed across sex, suggesting almost 1 player per two handball teams will suffer an ACL injury over the course of a season (Myklebust, Skjølberg, and Bahr 2013). Rugby also presents with a significantly high incidence of injury with 0.25 and 1.31 per 10,000 athlete exposures in men and women (Peck et al. 2013). Furthermore, higher rates of ACL injury in rugby have been reported in pooled meta-analyses, with females demonstrating an overall incidence of 0.36 per 1,000 competitions or practices and males having an incidence of 0.18 (Prodromos et al. 2007).

College-aged female soccer, basketball, team handball, rugby, and lacrosse athletes represent a population at high risk for sustaining a noncontact ACL injury.

ACL Injury Incidence as a Function of Sex, Sport, and Level of Play or Age

The sex disparity in injury incidence is perhaps one of the most highlighted epidemiological features of sport-related ACL injury research (Prodromos et al. 2007). Initial reports and subsequent reviews implicated an overall higher incidence of ACL injury in the female athlete when compared to their male counterparts (Arendt and Dick 1995; Myklebust et al. 1997; Myklebust and Bahr 2005; Messina, Farney, and DeLee 1999; Shea et al. 2004). The notion that females were between 2 (Myklebust et al. 1997) and 4 times (Arendt and Dick 1995) greater risk for sustaining a ACL injury was generalized across sports and levels of play / age groups (Renstrom et al. 2008; Renström 2013). However, these initial epidemiological studies focused on a sex disparity in ACL injury incidence between three specific sports; soccer (Arendt and Dick 1995; Shea et al. 2004), basketball (Arendt and Dick 1995; Messina, Farney, and DeLee 1999), and team handball (Myklebust et al. 1997).

The rationale for comparing ACL injury incidence between males and females in these three sports was sound, as soccer, basketball, and team handball represent sports with high levels of participation and substantially higher ACL injury rates over other team sports (Agel, Arendt, and Bershadsky 2005; Hootman, Dick, and Agel 2007; Swenson et al. 2013; Joseph et al. 2013; Cumps et al. 2008). In collegiate-level soccer, females were identified to have over 3 times the risk of males for sustaining a noncontact ACL injury (Arendt and Dick 1995). A higher prevalence of ACL injury was also observed in insurance data from adolescent soccer athletes, with ACL injury representing 37% and 24% of all knee injuries for males and females (Shea et al. 2004). Similarly, competitive female team handball athletes were at an overall 2-fold

increased risk of ACL injury compared to males, with 90% of ACL injuries sustained by a noncontact mechanism (Myklebust et al. 1997). The greatest sex disparity in ACL injury incidence was initially observed in collegiate and high school basketball. Female college basketball athletes were observed to be at 4 times greater risk for sustaining an ACL injury compared to males (Arendt and Dick 1995). As in soccer, the trend toward higher injury rates in females was reflected in younger athletes; female high school basketball athletes exhibited 3.79 times greater risk of sustaining a ACL injury compared to males (Messina, Farney, and DeLee 1999). While these earlier sport-related ACL injury epidemiology studies provided significant insight to a sex disparity in ACL injury incidence within specific sports, these initial studies did not consider the broader context of sport participation, and did not include sports such as rugby, hockey, lacrosse, men's football, volleyball, field hockey, wrestling, gymnastics, baseball, and softball. Thus the results from earlier sport-related injury epidemiology studies should not be interpreted such that all female athletes are at an overall higher risk for suffering an ACL injury across all sports and levels of participation.

More recently, high-quality, large-sample sport-related injury epidemiology studies and meta-analyses have been conducted across various levels of competition and have included a greater diversity of sports in order to provide a global perspective on ACL injury incidence. As these more recent studies have included more sports in their comprehensive analyses, the overall sport-related ACL injury incidence between males and females has been observed to be similar at both the youth (Straccolini et al. 2014) and high school (Joseph et al. 2013; Swenson et al. 2013) levels. ACL injury accounts for 10% of injury in male and 8.9% of injury in female youth athletes (Straccolini et al. 2014). In high school athletes the overall rate ratio between male and female ACL injury incidence ranged from 1.01 (Swenson et al. 2013) to 1.16 (Joseph et al.

2013), suggesting little difference between high school male ACL injury rates inclusive of 20 high school sports from 100 nationally representative schools in The United States.

While the overall ACL injury incidence between sexes is similar at the youth and high school athlete levels, a recent cohort study of college and high school-aged athletes by Beynnon et al. observed females to have a higher overall first-time noncontact ACL injury incidence compared to male athletes competing in the same sports at both the collegiate and high school levels (Beynnon et al. 2014). Beynnon et al.'s methodology was the first to simultaneously assess the effects of sex, sport, and level of play (high school & college) on first-time noncontact ACL injury incidence using a Poisson regression analysis. Interestingly, Beynnon et al. did not identify any significant interactions between the three demographic predictors for first-time noncontact ACL injury. Beynnon et al. observed their Poisson regression model to predict similar incidences of injury for male and female sports at both the college and high school level. The results of Beynnon et al.'s study implicate the observed overall adjusted 2.10-fold increased risk of first time noncontact ACL injury for females over their male counterparts is independent of sport and level of play (Beynnon et al. 2014). Additionally, Beynnon et al. observed a similar adjusted relative risk of 2.38 for first-time noncontact ACL injury in male and female college-level athletes compared to high-school athletes participating in the same sport. Furthermore, the relative risk for first-time noncontact ACL injury in Beynnon et al.'s cohort was higher for soccer (1.77) and rugby (2.23) athletes over lacrosse players independent of sex and level of play (Beynnon et al. 2014). The results of Beynnon et al.'s study are important; implicating an athlete's risk for sustaining a first-time noncontact ACL injury is independently influenced by their sex, level of sport participation, and type of sport. Thus, ACL injury risk estimates should not be overly generalized, and should not consider a single demographic predictor alone.

College-aged females are at greater risk for sustaining ACL injury compared to high school-aged female athletes (Beynnon et al. 2014; Prodromos et al. 2007). Female college-aged athletes are at substantially higher risk of ACL injury compared to their male counterparts participating in the same sport (Beynnon et al. 2014; Prodromos et al. 2007). As previously discussed, sex and level of competition are not the only factors to consider when identifying a population at high risk for sustaining a noncontact ACL injury. Rugby, team handball, basketball, and soccer represent four sex-comparable team sports that require rapid changes in direction, cutting / pivoting, and landings with significant disparity in ACL injury rates between college-aged males and females. In descending order the female-to-male ratios of injury incidence are as follows: rugby (5.3 (Peck et al. 2013)), team handball (5.01 (Myklebust et al. 1998)), basketball (3.63 (Agel, Arendt, and Bershadsky 2005; Mihata, Beutler, and Boden 2006)), and soccer (2.67 (Agel, Arendt, and Bershadsky 2005; Mihata, Beutler, and Boden 2006)). While rates of injury do not appear to significantly differ between college-aged male and female lacrosse athletes the ACL injury incidence in women's collegiate lacrosse has been reported to range from 0.18 to 0.221 per 1,000 person-practices or competitions (Mihata, Beutler, and Boden 2006; Beynnon et al. 2014), and exhibit a relatively low incidence compared to college women's soccer and basketball (Mihata, Beutler, and Boden 2006), women's lacrosse represents a sport currently experiencing exponential growth (US Lacrosse, 2013). Increases in sport participation are associated with increased injury prevalence (Conn, Annest, and Gilchrist 2003; Ferguson, Green, and Hansen 2013), thus as a sport that requires rapid changes in direction and fast-paced cutting / pivoting, motions associated with noncontact ACL injury mechanics (Shultz et al. 2012; Boden et al. 2000), female college-aged lacrosse athletes represent a population that has the potential to significantly contribute to the burden of ACL injury.

The Influence of Workload, Time-of-Season, Phase-of-Play, and Training & Competition Activity on Injury Incidence in Sport

Epidemiological evidence supports a link between higher magnitude cumulative and acute training loads and injury incidence in sport participation (Finch, Williamson, and O'Brien 2011). However the underlying mechanisms that influence a higher incidence of injury secondary to high training load exposure are not well understood. Previous literature has described sport injury incidence in the context of workloads and rest breaks (training load), time-of-season, phase-of-play, and activity session type (training versus competition) effects (Finch, Williamson, and O'Brien 2011).

Higher Magnitude Training Loads Throughout a Sport Season are Associated with an Increased Injury Incidence

Elevations in training loads throughout a season represent periods of higher-intensity work and activity congestion in which physical activity demands are higher relative to athlete conditioning / fitness and recovery capacity such as pre-season training when conditioning and fitness development are commonly a training goal (Gabbett 2000; Gabbett and Jenkins 2011; Gabbett and Domrow 2007). Similarly, training loads may increase during post-season play when competition congestion can occur in combination with higher work intensities due to increased levels of play (Gabbett 2000; Gabbett and Jenkins 2011; Gabbett and Domrow 2007). During periods of high training load exposure, the acute and cumulative influence of fatigue is hypothesized to drive observed increases in athletic injury incidence (Gabbett 2000; Gabbett and Jenkins 2011; Gabbett and Domrow 2007; Colby et al. 2014; Finch, Williamson, and O'Brien 2011). The definition of exercise-induced fatigue is complex and incorporates multiple interacting central and peripheral physiological factors that influence an

individual's exercise performance (Knicker et al. 2011). While exercise or sport performance is implicated to be decreased in a fatigued state, direct and objective quantification of exercise-induced fatigue is difficult due to the multiple interacting factors that contribute to exercise-induced fatigue (Knicker et al. 2011; J. M. Davis 1995). Although training load studies do not directly evaluate the influence of or quantify fatigue mechanisms regarding sport-related injury risk, training load measures represent indirect surrogate markers of fatigue during a single session of sport participation or cumulatively throughout a sport season (Gabbett 2000; Gabbett and Jenkins 2011; Gabbett and Domrow 2007; Colby et al. 2014; Finch, Williamson, and O'Brien 2011). To date, multiple studies have identified seasonal periods with higher training loads to be associated with a higher sport-related injury incidence (Gabbett 2000; Gabbett and Jenkins 2011; Gabbett and Domrow 2007; Colby et al. 2014; Finch, Williamson, and O'Brien 2011). Considering training load markers as indirect or surrogate markers of fatigue, it is hypothesized that high levels of exercise-induced fatigue are linked to an elevated injury risk, especially in high-risk athlete populations.

In 2001 Foster et al. described session rate of perceived exertion (RPE) multiplied by session duration (minutes) to be a valid estimate of training load during non-steady state exercise with periods of undulating intensities such as interval training, team sport competition, and practices (Foster et al. 2001). Foster et al's. method of training load calculation has been identified to correlate with markers of total body physiological and mechanical system stress in response to exercise exposure, and has been adopted as a measure of *internal training load* (Foster et al. 2001; Wallace, Slattery, and Coutts 2014; Slattery et al. 2012).

While individual markers of total body physiological and mechanical system stress may explain underlying mechanisms responsible for injury during sport participation, Foster et al's

internal training load metric is the only marker identified to consistently correlate with injury rates over the course of a sport season (Gabbett and Domrow 2007; Gabbett 2004b; Gabbett and Jenkins 2011). While internal training load has not been regularly measured in all sport-related injury epidemiology studies, internal training load and injury incidence exhibits a strong correlation in both competition and practice / training activity in sport. Gabbett et al. has observed a strong, positive ($r=0.86$) correlation between internal training load and injury incidence throughout a sport season (Gabbett 2004b). Gabbett et al. noted a substantially higher weekly internal training load was associated with a higher incidence of injuries during the preseason period of a rugby season (Gabbett 2004b). In addition to the acute effects of a higher internal training load during the preseason period of a sports team's season, Gabbett et al. also observed a potential cumulative effect of higher training loads toward the end of a rugby season, with the highest injury incidence of through the season of 195.5 per 1,000 athlete exposures (Gabbett 2000).

Similar cumulative effects have been observed in other sports such as soccer (Hägglund, Waldén, and Ekstrand 2005). Comparing a cohort of elite Swedish soccer athletes to a cohort of elite Danish athletes, Hägglund et al. observed a higher incidence of injury during the Swedish cohort's preseason, which was characterized as a longer duration of higher-intensity training compared to the Danes' (Hägglund, Waldén, and Ekstrand 2005). Furthermore, a significant effect of preseason training load on injury incidence is evident. Gabbett compared the injury incidence between three consecutive preseasons (2001, 2002, & 2003) in a rugby league. During each subsequent season the training load was decreased (2001-highest training load, 2003-lowest training load). Gabbett observed an effect of training load on injury incidence, with the highest training load season being associated with an incidence of 156.7 injuries per 1,000 training

hours, and the lowest training load preseason with an incidence of 78.4 injuries per 1,000 training hours, effectively decreasing injury incidence by 50% (Gabbett 2004b). Furthermore, Gabbett observed no detrimental impact of training load reduction on athletic performance improvements over the course of the consecutive preseasons. Interestingly, Gabbett observed a potential performance-enhancing effect of the lowest training-load during the 2003 season. During the low-load 2003 preseason athletes exhibited a 76% probability of a physiologically significant improvement in power output and a 62-88% probability of a physiologically significant improvement in aerobic fitness over the high-load 2001 preseason increases in athletic performance variables (Gabbett 2004a).

A majority of training load literature has focused on the preseason period. The training stimulus during the preseason is unique in such that it must act as a stimulus to promote adaptation that results in physical fitness / performance enhancement while concomitantly be managed to consider the potential for deconditioning and a decreased recovery capacity of athletes coming into training from the off-season (Colby et al. 2014). If the training stimulus during the preseason is too low, athletes may not achieve physical fitness levels necessary to participate at a competitive level of play. Yet if the training stimulus is too high, athletes may be exposed to a training stimulus that they cannot manage, overstressing physiology and mechanical capacity of tissues (Teyhen et al. 2014; Wallace, Slattery, and Coutts 2014), resulting in a heightened risk of injury (Gabbett and Jenkins 2011; Johnston et al. 2013; Rogalski et al. 2013; Colby et al. 2014). Overall, training loads during the preseason are generally characterized to be high compared to the in-season and postseason training loads (Gabbett and Jenkins 2011; Gabbett 2008; Gabbett 2004b; Rogalski et al. 2013).

While multiple investigations have reported higher training loads during the preseason to be positively correlated with injury rates, epidemiological studies in multiple team sports also report higher incidences of injury across multiple sports during the preseason and a greater incidence in higher intensity competition play during the postseason compared to preseason and midseason competition (Hootman, Dick, and Agel 2007). College women soccer athletes have been observed to have the highest rate of injury compared to all NCAA sports during the preseason training period, with an incidence of 9.5 injuries per 1,000 athlete training sessions (Agel and Schisel 2013). Additionally college women's soccer, basketball, and lacrosse have significantly greater injury rate ratios of 3.3, 2.4, and 1.7 respectively compared to in-season practice injury incidences (Agel and Schisel 2013). Interestingly, Hootman et al. observed injury rates during postseason competition compared to preseason competition, yet observed lower practice injury incidence during postseason training compared to preseason training sessions (Hootman, Dick, and Agel 2007). Hootman et al. suggested that a lower training load generally characterizes postseason training sessions, while postseason competition carries a higher intensity and resultant training load, whereas preseason training loads during practice sessions are higher, and competition intensity during the preseason is lower. This reciprocal relationship between competition and practice session training loads between the preseason and postseason may explain the trends in injury incidence during the pre- and postseason (Hootman, Dick, and Agel 2007).

Previous findings implicate lower training loads are associated with decreased injury incidence. Furthermore, moderately lower preseason training loads promote performance-enhancing effects in team-sport athletes over higher preseason training loads. Thus, lower training load exposures appear dually beneficial for the team sport athlete, promoting

performance gains and reduced injury risk. The sum of epidemiological evidence suggests that training load is a strong determinant of injury and performance in sport. While lower training loads are linked to performance enhancement and decreased injury incidence, the underlying mechanisms responsible for such associations remain unknown. Training load measures are established surrogate markers of exercise-induced fatigue which are described to directly moderate muscle performance, motor skill, and ultimately competition or training performance in sport (Knicker et al. 2011). While previous studies have evaluated the association between training load and injury incidence, no studies have comprehensively evaluated the association between underlying physiological responses representative of exercise-induced fatigue and injury incidence or risk. We propose that individuals at high risk for injury may demonstrate different biomechanical and biochemical responses to exercise-induced fatigue exposure compared to individuals with a lower risk injury.

Competition Play is Associated with Higher Injury Incidences Compared to Training Sessions

There is a significantly greater risk for sustaining an ACL injury during competition compared to practice activity (Hootman, Dick, and Agel 2007). While the primary cause for a higher injury incidence during competition has not been specifically identified, the theory that exposure to a higher acute training load or workload intensity during competition compared to practice sessions warrants support as a plausible explanation that deserves further investigation. Evidence suggests that competition loads are substantially higher compared to practice workloads

(Dawson et al. 2004; Montgomery, Pyne, and Minahan 2010; Colby et al. 2014; Finch, Williamson, and O'Brien 2011). While a cause and effect relationship between high and low training loads and injury has not been established during competition as in practice sessions

(Gabbett 2004a), a strong positive association ($r = 0.86$) between training load and match injury has been identified (Gabbett 2004b). Furthermore, there is support that preseason competition training loads are lower compared to in-season and postseason training loads, with higher rates of in-season and postseason competition injuries compared to preseason competition-related injury rates (Gabbett and Domrow 2007; Colby et al. 2014; Rogalski et al. 2013).

The effects of a higher training load exposure on competition and practice injury rates in sport may be an underlying factor contributing to a greater injury incidence during high load competition and practice activities. Improving an athlete's physiological and biomechanical response to high training load exposure or reducing their level of exercise-induced fatigue may be a viable avenue for intervention to promote a reduction in injury incidence during characteristically higher-intensity competition and practice periods in athletics. Future research is necessary to understand the interaction between higher intensity training load exposure and modifiable risk factors for ACL injury such as high-risk lower extremity biomechanics which can be modified to substantially decrease ACL injury risk in the active population (Sadoghi, Keudell, and Vavken 2012).

Exercise-induced fatigue appears to be an underlying factor influencing sport-related injury rates during single sport training or competition sessions as well as during extended periods of high physical demands that exceed the recovery capacity of the athlete. Female college-aged soccer, basketball, rugby, team-handball, and lacrosse athletes represent a population at elevated risk for sustaining noncontact ACL injury. To date, no research has evaluated the impact of fatigue on an individual's physiological response and injury risk in a population already at high risk for sustaining a noncontact ACL injury. Future research evaluating how high-risk individuals respond to high-intensity exercise-induced fatigue exposure

may provide insight into currently unknown factors that contribute to an elevated risk for noncontact ACL injury.

SECTION TWO: Biomechanical Mechanisms and Risk Factors for Sport-Related Noncontact ACL Injury

Biomechanics associated with sport-related noncontact ACL injury are the focus of the majority of the literature surrounding ACL injury. While there are other variables linked to noncontact ACL injury such as demographics, anatomical features, hormonal influences, and environmental considerations, biomechanical factors have been identified to be modifiable (Shultz et al. 2012), and thus represent a target for interventions aimed at reducing sport-related noncontact ACL injury. Previous literature has investigated noncontact ACL injury biomechanics with two primary analytical approaches, a mechanistic approach and a risk factor approach (Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a).

The mechanistic approach is concerned with the investigation of biomechanics that are the consequence of self-imposed human motion that produces an excessive tension force across the ACL, leading to tissue failure, and ultimately rupture of the ligamentous tissue (Yu and Garrett 2007; Gianotti et al. 2009). The mechanistic approach leverages two primary avenues of study to investigate mechanisms associated with sport-related noncontact ACL injury, in-vitro / in-vivo loading studies and video analysis of injury episodes. Risk factor analysis methodology commonly takes the form of large-sample longitudinal prospective cohort studies, where participants' biomechanics during functional movement or athletic tasks are evaluated prior to injury events (Padua 2010). ACL injuries are recorded while the cohort is followed for multiple years succeeding the initial biomechanical screening. As sufficient injury data is gathered over

the course of the study it is possible to determine if certain baseline biomechanical profiles are significant predictors of injury (Portney & Watkins, 2008). Numerous investigations have identified mechanisms (Kobayashi et al. 2010; Shimokochi and Shultz 2008; Dai et al. 2012) of injury as well as significant risk factors (Dai et al. 2012; Zebis et al. 2009; Hughes and Watkins 2006; Zazulak et al. 2007; Shultz et al. 2012) predictive of injury in the female athlete population.

When evaluating sport-related noncontact ACL literature it is important to distinguish between a risk factor and a mechanism of injury. A mechanism of noncontact ACL injury is linked to the injury event and in-vitro / -vivo loading of the ACL, whereas a risk factor is predictive of injury (Portney & Watkins 2008)(Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a). While mechanisms of ACL injury are known to result in high tensile forces in the ligament and may lead to ultimate tissue failure during an injury event, mechanisms may not be significant predictors of injury, and therefore may not be risk factors for sustaining an ACL injury. Conversely, risk factors for noncontact ACL injury may not contribute to significant development of high-tension forces in the ligament or may not be observed at the time of an injury event, thus risk factors may not be classified as injury mechanisms. While some biomechanics associated with noncontact sport-related ACL injury are classified as both mechanisms and risk factors, one must interpret the literature with caution, as risk factors and mechanisms of injury are inherently different. The remainder of this review aims to highlight biomechanics that are associated with sport-related noncontact ACL injury as either risk factors or mechanisms for / of injury in athletes. Evaluation of biomechanical variables that are associated with noncontact ACL injury in a high-risk athlete population such as female college-aged field and court sport athletes will provide insight into factors that explain female athletes

elevated risk of injury during sport participation. Furthermore, investigating how biomechanical variables linked to noncontact ACL injury respond to exercise-induced fatigue in female college-aged field and court sport athletes may lend a better understanding of the underlying mechanisms responsible for an increased injury incidence in this population.

Sagittal Plane Knee, Hip, and Trunk Biomechanics Associated with Noncontact ACL Injury

The following section of this review will describe sagittal plane lower extremity biomechanics that have been identified as variables associated with sport-related noncontact ACL injury mechanisms and risk factors. This information provides insight into specific biomechanical variables to consider in a high-risk athlete within the context of exercise-induced fatigue exposure in order to evaluate variables that may have the strongest influence on injury-risk. Sagittal plane joint motion and neuromuscular control represents the primary plane of energy absorption and force generation during sport participation (Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013b). Developing an understanding regarding the influence of exercise-induced fatigue on sagittal plane biomechanics during athletic motions incorporating landings and rapid changes in direction will provide insights that may explain variation in sport-related noncontact ACL injury mechanisms and risk factors during high-intensity sport activity participation.

Sagittal Plane Knee Biomechanics

Anterior tibial shear force results in an anterior translation of the tibia relative to the femur and is consistently reported as the primary force to result in the greatest magnitude load aggregation in the ACL (Shimokochi and Shultz 2008; Dai et al. 2012; Markolf et al. 1995; Yu and Garrett 2007). While anterior tibial shear force results in the greatest direct ACL loading,

anterior tibial shear force is not a biomechanical load that is directly moderated by a single neuromuscular control strategy (Markolf et al. 1995; Yu and Garrett 2007). anterior tibial shear force is a resultant linear anterior shearing force that ensues across the knee articulation as a component of quadriceps force application through the patellar tendon (Herzog and Read 1993). Quadriceps force production generates internal knee extension moment about the knee joint in resistance to external vertical and posterior ground reaction forces that would otherwise induce knee flexion during accelerations associated with changing direction in sport activity, such as landing, jumping, or cutting (Herzog and Read 1993; Arms et al. 1984; Draganich and Vahey 1990; Yu and Garrett 2007).

There is no neuromuscular control strategy that is directly responsible for inducing high levels of anterior tibial shear force across the knee joint, however, combinations of quadriceps force application, varying knee joint flexion angles and ground reaction forces appear to moderate anterior tibial shear force in-vivo and in-vitro (Markolf et al. 1995; Fleming et al. 2001; Withrow, Huston, Wojtys, and Ashton-Miller 2006a; Yu and Garrett 2007). High-magnitude quadriceps force application applied at shallow knee flexion angles has been reported to induce the largest resultant anterior tibial shear force at the knee joint, and subsequently the largest magnitude ACL loading (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006a). Alternatively, quadriceps force application at deeper knee flexion angles greater than 30° - 40° has been implicated to mitigate resultant high anterior tibial shear force generation and subsequent ACL loading, due to the increased potential for a compressive and decreased anterior shearing component of the patellar tendon force across the tibiofemoral joint (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006a; Arms et al. 1984; Herzog and Read 1993; Dai et al. 2012; Yu and Garrett 2007). anterior tibial shear force may be further

reduced when the knee assumes flexion angles beyond 60° - 70° due to the ability of the hamstring musculature to induce a posterior shear force across the tibiofemoral joint at their distal attachments to the posterior tibia (Fujiya et al. 2011; Dürselen, Claes, and Kiefer 1995). While there is some debate surrounding the ability of the hamstrings to reactively respond to rapid anterior tibial shear force application in-vivo (Shimokochi and Shultz 2008; Yu and Garrett 2007), increases in hamstring muscle stiffness at deeper knee flexion angles (Blackburn et al. 2013) and decreases in hamstring length secondary to greater hip flexion postures (Withrow et al. 2008) have been implicated to reduce anterior tibial shear force. While anterior tibial shear force is not the only force that can induce ACL loading, it appears to induce the highest magnitude loading within the ACL tissue (Shimokochi and Shultz 2008; Yu and Garrett 2007; Dai et al. 2012). Furthermore, anterior tibial shear force resulting from aggressive quadriceps force application at a shallow knee flexion angle (<30°) is the only isolated internally generated (within physiological limits) resultant force implicated to induce loads high enough to result in ACL rupture (DeMorat 2004). Sagittal plane lower extremity biomechanics indirectly moderate anterior tibial shear force.

A shallow knee flexion angle (<30°) is consistently reported as one of the most prominent knee postures reported during injury events (Krosshaug, Nakamae, et al. 2007; COCHRANE et al. 2007; Koga et al. 2010) and significantly contributes to increases in anterior tibial shear force in-vivo (Beynnon et al. 1995) and in-vitro (Markolf et al. 1995) with concurrent application of quadriceps force across the knee joint. While, shallow knee flexion angles appear to be linked to a noncontact injury mechanism, there is a lack of published prospective cohort study literature that directly implicates a shallow knee flexion angle at the initial stages of landing to be a significant predictor of primary ACL injury (Smith et al. 2012). While no prospective studies

have identified a shallow knee flexion angle ($<30^\circ$) to be predictive of ACL injury, Hewett et al. observed 10° less peak knee flexion angle during the loading phase of a drop-jump task in injured ($n=9$) (71.9°) females compared to their uninjured (82.4°) counterparts in a cohort of 205 female soccer, basketball, and volleyball athletes (Hewett et al. 2005). The results of Hewett al's. 2005 study are important, but should be interpreted with caution, as the results are based on a sample with a limited number of injuries, and peak knee flexion angle alone was not predictive of ACL injury in this cohort (Hewett et al. 2005).

Although a shallow knee flexion angle during the initial energy absorption phases of landing has not yet been identified as a prospective risk factor for noncontact sport-related ACL injury, many intervention studies that deploy neuromuscular training programming aimed at reducing knee injury emphasize landing and performing athletic tasks with knee flexion angles greater than 30° effectively reduce ACL injury incidence (Postma and West 2013; Noyes and Barber-Westin 2014; Benjaminse et al. 2014; Sadoghi, Keudell, and Vavken 2012).

Neuromuscular training programs and feedback aimed at increasing sagittal plane knee angle during athletic participation effectively increase knee flexion angles during landing maneuvers (Postma and West 2013; Noyes and Barber-Westin 2014; Benjaminse et al. 2014). While there is no concurrent evidence that illustrates injury prevention programming increases knee flexion angle and reduces injury rates, indirect evidence from intervention studies suggests increases in knee flexion angle may decrease an individual's risk of sustaining an ACL injury during sport participation. Future prospective intervention studies that evaluate the effects of interventions on biomechanics and injury rates in parallel are necessary to establish shallow knee flexion as a prospective risk factor linked to noncontact sport-related ACL injury.

Quadriceps muscle force applied through the patellar tendon results in the effective internal knee extensor mechanism and produces an internal knee extension moment (Winter 2009). Internal net knee extension moment is the primary muscle-generated torque that resists externally generated knee flexion moment as the ground reaction force vector acts across the knee joint (Winter 2009). The vertical and posterior components of the ground reaction force vector have the capacity to induce an external knee flexion moment about the knee articulation (Withrow, Huston, Wojtys, and Ashton-Miller 2006a; Winter 2009). In order to prevent the knee from collapsing into maximal flexion or to decelerate the knee moving toward flexion during landing or cutting during sport, the quadriceps musculature must generate an appropriate internal knee extensor moment about the knee joint via eccentric force production (Withrow, Huston, Wojtys, and Ashton-Miller 2006a).

The effective knee extensor mechanism's moment arm is variable throughout the sagittal plane arc of motion, achieving its maximal length at approximately 45° of knee flexion, with moment arm length minimized below 30° of knee flexion, toward extension (Krevolin, Pandy, and Pearce 2004; Tsaopoulos, Baltzopoulos, and Maganaris 2006). In order to counter the external knee flexion moment induced by the ground reaction force vector, quadriceps muscle force production at shallow knee flexion angles must be greater than quadriceps force production at deeper knee flexion angles in order to compensate for the shorter moment arm of the knee extensor mechanism between 0° – 40° of knee flexion (Krevolin, Pandy, and Pearce 2004; Tsaopoulos, Baltzopoulos, and Maganaris 2006). Aggressive quadriceps force production at a shallow knee flexion angle that is generated in order to produce a substantial internal knee extension moment in resistance to external knee flexion moment can impart anterior tibial shear force that results in injurious loading of the ACL (DeMorat 2004) due to the larger anterior shear

component of the patellar tendon force vector at a shallow knee flexion angle less than 30° - 40° of knee flexion (Nunley et al. 2003; Shimokochi and Shultz 2008; Yu and Garrett 2007; DeMorat 2004). While internal knee extensor moment is not directly measurable at the time of injury through observational analyses, cadaveric studies implicate that large knee extensor moments generated at a shallow knee flexion angle can induce anterior tibial shear force that imparts injurious loads on the ACL (DeMorat 2004; Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006a). Thus generation of similar knee extension moment through an increased moment arm is ideal to reduce anterior tibial shear force (Yu and Garrett 2007; Shimokochi and Shultz 2008), and can be achieved through a neuromuscular control strategy that promotes a deeper knee flexion angle during athletic participation.

Sagittal Plane Lumbopelvic Hip Complex Biomechanics

The lumbopelvic hip complex is the segmental link between the lower extremity subsystem and the upper body (Patla, Ishac, and Winter 2002; Patla, Adkin, and Ballard 1999). The whole body center of mass is approximately located within the center of the trunk segment (Winter 2009). The lumbopelvic hip complex incorporates the lumbar spine - pelvis segmental link within the kinetic chain (Horak and Nashner 1986; Iqbal and Pai 2000). During locomotion, the center of mass position is influenced by trunk angular acceleration (Nott et al. 2010). Trunk angular accelerations are influenced by net joint moments acting on the kinetic chain to maintain static or dynamic posture during human motion (Iqbal and Pai 2000; Horak and Nashner 1986; Nott et al. 2010). High-magnitude accelerations of the center of mass result in rapid changes in direction of travel (Vallis, Patla, and Adkin 2001; Patla, Ishac, and Winter 2002; Patla, Adkin, and Ballard 1999; Patla et al. 1991) such as side-step cutting, pivoting, and landing from a jump, identified mechanisms of sport-related noncontact ACL injury (Shultz et al. 2012).

Similar to the study of knee joint biomechanics associated with ACL injury, lumbopelvic hip complex biomechanics are evaluated using a mechanistic and risk factor approach. Current evidence has described sagittal plane lumbopelvic hip complex posturing during sport-related noncontact ACL injury events (Krosshaug, Nakamae, et al. 2007; Boden et al. 2000; Boden et al. 2009; Hewett, Torg, and Boden 2009; Sheehan, Sipprell, and Boden 2012) and has described the influence of sagittal plane trunk kinematics on sagittal plane lower extremity biomechanics associated with ACL injury (Kulas et al. 2008; Kulas, Hortobágyi, and DeVita 2010; Kulas, Hortobágyi, and DeVita 2012; Blackburn and Padua 2008; Blackburn and Padua 2009; Jamison, Pan, and Chaudhari 2012; Frank et al. 2013). While cadaveric and injury event observation / analyses methods are commonly used to study the influence of knee joint biomechanics on ACL loading and injury mechanisms, lumbopelvic hip complex literature focuses on injury event data and in-vivo biomechanical modeling studies that provide insight regarding hip and trunk biomechanics that are indirectly linked to knee loading mechanisms that may directly load the ACL. In addition to a mechanistic approach, prospective cohort studies have included evaluations of lumbopelvic hip complex neuromuscular control as a risk factor for sport-related noncontact ACL injury. The following portion of this review will describe sagittal plane hip and trunk kinematics identified at the time of injury, and will discuss the influence of lumbopelvic hip complex neuromuscular control on sagittal plane knee biomechanics previously linked to ACL loading mechanisms and injury events.

Evaluation of video data has provided insight regarding sagittal plane trunk and hip kinematics during noncontact ACL injury events (Krosshaug, Slauterbeck, et al. 2007; Krosshaug, Nakamae, et al. 2007; Boden et al. 2009; Hewett, Torg, and Boden 2009; Sheehan, Sipprell, and Boden 2012; Boden et al. 2000). There is a general consensus that the trunk

assumes a relatively upright or extended position during injury events, however there is substantial variability in descriptions of sagittal plane hip kinematics at the time of injury (Krosshaug, Slauterbeck, et al. 2007; Krosshaug, Nakamae, et al. 2007; Boden et al. 2009; Hewett, Torg, and Boden 2009; Sheehan, Sipprell, and Boden 2012; Boden et al. 2000). While the sagittal plane hip position during injury events is generally described to be flexed, descriptions of the magnitude of hip flexion during injury episodes varies from as small as 19° (Krosshaug, Slauterbeck, et al. 2007) to over 54° (Boden et al. 2009). The large range in observed hip flexion angles during injury is likely attributable to differences in methodology used for the hip angle calculation. In review of the current literature, three primary methods of measurement of sagittal plane hip kinematics have emerged. The most common methodology used to describe the hip position during injury is reporting the angle formed by the vertex of the thigh segment and trunk (Boden et al. 2009; Hewett, Torg, and Boden 2009; Krosshaug, Nakamae, et al. 2007). While the thigh-trunk segment angle provides some insight regarding the sagittal plane hip position during injury, it excludes the anatomical consideration of the pelvis, the lower extremity subsystem's link to the upper body and the location true anatomical hip joint (Krosshaug, Slauterbeck, et al. 2007), the femoroacetabular joint. Thus, estimation of the hip - trunk segment angle may not adequately represent the sagittal plane position of the hip joint at the time of injury. Krosshaug et al. and Koga et al. have employed a video-matching skeletal modeling technique to better estimate bony anatomy kinematics from video data (Koga et al. 2011; Koga et al. 2010; Krosshaug, Slauterbeck, et al. 2007). The biomechanical modeling techniques establish the hip joint as the femur - pelvis segment link, which is more representative of lumbopelvic hip complex anatomy than the thigh - trunk angle alone (Krosshaug, Slauterbeck, et al. 2007).

While modeling and video analysis techniques offer valuable information regarding hip kinematics during injury events, Sheehan et al. offers a novel mechanistic approach in evaluating the influence of sagittal plane lumbopelvic hip complex kinematics during noncontact ACL injury (Sheehan, Sipprell, and Boden 2012). Sheehan et al. compared video data of sagittal plane trunk kinematics between individuals who suffered noncontact ACL injury and matched controls. Instead of measuring the thigh - trunk angle or apply a biomechanical model to the video data, Sheehan et al. evaluated trunk and hip biomechanics as segment angles relative to the gravitational vector (vertical) acting on the whole body center of mass, thus trunk and hip angles were evaluated independently. Sheehan et al. then estimated the distance between the center of mass and base of support normalized to femur length (Sheehan, Sipprell, and Boden 2012). Independent evaluation of the thigh and trunk kinematics offers insight regarding each segment's contribution to the noncontact ACL injury mechanism. Sheehan et al's. hypothesis incorporates the influence of the position of the center of mass relative to the base of support during rapid motion as in sport, when the center of mass can be accelerated to a position outside of the base of support, resulting in a scenario of dynamic instability that must be countered by the influence of internally generated joint moments across the kinetic chain to establish dynamic stability to prevent a fall (Sheehan, Sipprell, and Boden 2012; Iqbal and Pai 2000). When the distance between the base of support and center of mass increases, there is a greater influence of the gravity vector to promote instability on the kinetic chain which can result in falling (Horak and Nashner 1986; Iqbal and Pai 2000). In order to resist falling, the center of mass is accelerated toward the base of support, via joint moments throughout the kinetic chain (Nott et al. 2010).

The results of Sheehan et al's. study indicated that individuals who sustained an injury exhibited a greater femur - gravity vector (equal and opposite force vector to vertical ground

reaction force vector) angle ($48 \pm 12^\circ$) compared to matched controls ($31 \pm 22^\circ$) with a mean difference of 16° greater angulation between the gravity vector and the femur/thigh angle. Additionally, uninjured matched controls had greater forward flexion; greater trunk - gravity vector angle ($16 \pm 13^\circ$) compared to the individuals who suffered ACL injury ($4 \pm 14^\circ$), with a mean difference of 12° less angulation between the gravity vector and trunk segment. Most notably Sheehan et al. observed an increased distance between the center of mass and Bos of almost one femur length (0.9 femur length) between the injured (1.5 ± 0.5) and uninjured (0.7 ± 0.7) individuals. Combined with biomechanical modeling studies that provide insight regarding the influence of sagittal plane trunk and hip biomechanics on knee loading, Sheehan et al.'s observations enhance understanding of the role of lumbopelvic hip complex kinematics during noncontact ACL injury.

Laboratory-based biomechanical analysis of sagittal plane lumbopelvic hip complex biomechanics during landing and squatting tasks support Sheehan et al.'s. results interpretation, suggesting a greater center of mass – base of support distance influences knee loading during athletic activities (Blackburn and Padua 2008). Sheehan et al. concludes that a when the thigh segment - gravity vector angle approaches perpendicular (90°), the more posteriorly displaced the center of mass is relative to the base of support (Sheehan, Sipprell, and Boden 2012). Compounding the effect of a greater thigh segment - gravity vector angle, a trunk - gravity vector angle that is toward extension (-) versus forward flexed (+), further posteriorly positions the center of mass relative to the base of support (Sheehan, Sipprell, and Boden 2012) increasing moment demand across the lower-extremity sub-system in order to maintain dynamic stability (Kulas et al. 2008; Kulas, Hortobágyi, and DeVita 2010; Kulas, Hortobágyi, and DeVita 2012; Sheehan, Sipprell, and Boden 2012).

In agreement with Sheehan et al.'s findings, numerous studies evaluating the influence of sagittal plane lumbopelvic hip complex biomechanics on knee loading implicate that a more posterior positioned center of mass relative to the base of support exacerbates knee biomechanics associated with ACL loading (Blackburn and Padua 2008; Blackburn and Padua 2009; Kulas, Hortobágyi, and DeVita 2012). Blackburn & Padua observed increasing forward trunk flexion versus a preferred sagittal plane trunk angle during double-leg drop landings concomitantly increases peak knee flexion (flexed: $96 \pm 21^\circ$ vs. preferred: $48 \pm 21^\circ$) and hip - pelvis angles (flexed: $71 \pm 19^\circ$ vs. preferred: $40 \pm 20^\circ$) during the loading phase of a jump landing (Blackburn and Padua 2008). Interestingly, Blackburn and Padua did not observe differences in knee flexion angle at initial ground contact between forward flexion and preferred conditions, however a greater hip flexion angle at initial ground contact was observed in the flexed position ($20 \pm 12^\circ$) versus the preferred ($14 \pm 12^\circ$). While a greater knee flexion angle and elevated hamstring force at initial ground contact or pre-ground contact may improve the capacity of the hamstring musculature to exert a posterior shearing force on the tibiofemoral joint (Zebis et al. 2009; Zebis et al. 2008; Walsh et al. 2012), a combined forward trunk flexion and hip flexion posture may pre-tension and improve activation of the hamstrings (Kulas, Hortobágyi, and DeVita 2010), affording the potential for resistance to anterior tibial shear force from effective knee extension forces applied at shallow knee flexion angles (Withrow et al. 2008; Fujiya et al. 2011). When quadriceps force is applied across the knee joint in a more flexed position, the anterior shearing component of the patellar tendon force is reduced, reducing anterior tibial shear force, thus mitigating the potential for injurious ACL loading (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006a; Dürselen, Claes, and Kiefer 1995; Draganich and Vahey 1990).

While Blackburn and Padua did not evaluate quadriceps or hamstring muscle activity in their 2008 study, they deployed a similar methodology to evaluate the effects of a flexed versus preferred trunk positioning on ground reaction forces and quadriceps muscle activation levels (surface electromyography) during single-leg drop landings (Blackburn and Padua 2009). Blackburn and Padua observed decreases in quadriceps muscle activity as well as vertical ground reaction force in the forward flexion condition position compared to the preferred condition (Blackburn and Padua 2009). Thus, it appears the results from Blackburn and Padua's biomechanical and neuromuscular control drop landing studies support Sheehan et al's explanation of the influence of sagittal plane lumbopelvic hip complex kinematics on noncontact ACL injury mechanisms, suggesting a greater posterior positioning of the center of mass relative to the base of support increases presence of sagittal plane factors associated with ACL loading mechanisms such as high levels of quadriceps muscle activity applied at shallow knee flexion angles (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006a; Dürselen, Claes, and Kiefer 1995; Draganich and Vahey 1990). Interpretation of the results from Blackburn and Padua combined with Sheehan et al's implicate that a lumbopelvic hip complex posturing that minimizes the distance between base of support and the gravity vector acting through on center of mass results in a decrease of the vertical ground reaction force magnitude and it's flexion moment arm length at the knee joint. Thus, there is a decrease in internal knee extension moment requirement and subsequent quadriceps force required to maintain dynamic equilibrium, or deceleration of the knee joint toward flexion during energy absorption.

These studies offer insight regarding the influence of sagittal plane lumbopelvic hip complex kinematics on lower extremity biomechanics and neuromuscular control; however, they did not report the influence of sagittal plane trunk motion on knee loads directly linked to ACL

loading such as knee extension moment or anterior tibial shear force. Work by Kulas et al. (Kulas et al. 2008; Kulas, Hortobágyi, and DeVita 2010; Kulas, Hortobágyi, and DeVita 2012) extends this research by examining the effects of sagittal plane trunk motion strategies when participants performed drop landings with an added 10% bodyweight force to their trunk. Participants either adopted a trunk forward flexion or trunk extension strategy versus their preferred trunk motion during the double-leg landings with added trunk loads (Kulas et al. 2008). While both the forward flexion and the extension groups experienced greater biomechanical demands at the knee and ankle during the added trunk load condition, the trunk extension strategy group experienced increases in knee extension and ankle plantarflexion angular impulses and energy absorption by 14-28%, whereas the trunk flexion group only experienced 4-9% increases (Kulas et al. 2008). Furthermore, the forward flexion group increased hip extensor energy absorption and angular impulse by 14-19%, whereas the trunk extensor group reduced hip extension efforts by 11-18% (Kulas et al. 2008).

Kulas et al.'s results suggest the trunk flexion group redistributed energy absorption to the hip joint, while the trunk extensor group re-distributed energy absorption to the knee, as their knee extension efforts increased relative to hip extension efforts (Kulas et al. 2008). Using a similar methodology, Kulas et al. compared estimates of anterior tibial shear force, quadriceps, hamstring, and gastrocnemius forces between trunk extensor and forward flexion adoption strategies. Individuals who adopted a trunk extension strategy increased peak anterior tibial shear force by 17% and average anterior tibial shear force by 35%, whereas the trunk flexion group did not experience increases in anterior tibial shear force during the drop-landing with the 10% bodyweight added trunk load (Kulas, Hortobágyi, and DeVita 2010). Both the flexion and extension strategy groups experienced increases in quadriceps and gastrocnemius forces,

however there was no difference in quadriceps or gastrocnemius forces between groups (Kulas, Hortobágyi, and DeVita 2010). One of the most insightful findings from Kulas et al.'s 2010 study was the effect of sagittal plane trunk adaptation strategy on hamstring muscle force output. Individuals who adopted a trunk flexion strategy increased hamstring force output by 13%, whereas the trunk extensor group reduced hamstring force output by 16% compared to the preferred condition (Kulas, Hortobágyi, and DeVita 2010). The reduction of hamstring muscle force may explain the significant increases in anterior tibial shear force experienced in the trunk extension strategy group compared to the flexion strategy group, as there was an increase in quadriceps force without a concomitant increase in hamstring muscle force, a muscle force capable of resisting anterior tibial shear force versus the posterior shearing component of the hamstring muscle force at the tibiofemoral joint (Withrow et al. 2008). Collectively, the aforementioned findings suggest an extended trunk angle positioning the center of mass posterior the base of support and the lower extremity subsystem increases energy absorption requirements at the knee (Kulas, Hortobágyi, and DeVita 2010; Kulas et al. 2008), resulting in greater internal knee extension moment requirement, increasing quadriceps muscle force demand and resultant anterior tibial shear force with quadriceps muscle force applied at a shallower knee flexion angle, increasing ACL loading (DeMorat 2004; Dürselen, Claes, and Kiefer 1995).

A significant body of the literature has identified sagittal plane lumbopelvic hip complex biomechanics linked to ACL injury mechanisms (Shimokochi and Shultz 2008), however, there is no current evidence identifying a specific sagittal plane lumbopelvic hip complex biomechanical pattern or movement strategy as a prospective risk factor for noncontact ACL injury. While differences in sagittal plane lumbopelvic hip complex biomechanics have been identified between those who have previously suffered ACL injury and uninjured matched

controls (Orishimo et al. 2010; Noehren et al. 2014), it appears these biomechanical differences may emerge following ACL injury and surgical intervention (Goerger et al. 2014).

Summary of Sagittal Plane Knee and Lumbopelvic Hip Complex Biomechanics Associated with Sport-Related Noncontact ACL Injury

A relatively extended sagittal plane posture at the knee and lumbopelvic hip complex has been identified during sport-related noncontact ACL injury events (Boden et al. 2010) and is theorized to be linked to greater sagittal plane energy absorption and loading at the knee joint (Sheehan, Sipprell, and Boden 2012). The current body of the evidence agrees that anterior tibial shear force is a primary in-vitro ACL loading mechanism (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007). Previous literature establishes aggressive quadriceps force application at knee flexion angles less than 30° - 40° is capable of inducing anterior tibial shear force and consequent ACL loading that results in ligamentous failure (DeMorat 2004). Knee flexion angle modifies the capacity of the effective knee extensor mechanism to generate a stabilizing / resistant internal extension moment about the knee articulation (Krevolin, Pandy, and Pearce 2004; Herzog and Read 1993) in response to high external knee flexion moment exposure from high-magnitude accelerations characteristic of sport participation (Shultz et al. 2012). High-magnitude internal knee extension moment generation at a shallow knee flexion angle is associated with greater anterior tibial shear force and ACL loading, while knee extension moment application at knee flexion angles greater than 30° – 40° does not result in subsequent high-magnitude ACL loading (Shimokochi and Shultz 2008; Yu and Garrett 2007). High-magnitude internal knee extension moments and anterior tibial shear force are observed during energy attenuation strategies that reduce hip extension energy absorption and the capacity of the hamstring musculature to induce posterior shearing forces at the tibiofemoral joint (Kulas,

Hortobágyi, and DeVita 2010). Landing in a more upright trunk posture is associated with shallow knee flexion angles and hip angles (Blackburn and Padua 2008), positioning the trunk and center of mass more posterior to the lower extremity subsystem (Sheehan, Sipprell, and Boden 2012). A posterior positioning of center of mass increases energy absorption demands at the knee relative to the hip (Kulas, Hortobágyi, and DeVita 2010; Kulas, Hortobágyi, and DeVita 2012) driving increased quadriceps activity (Blackburn and Padua 2009) and force output (Kulas, Hortobágyi, and DeVita 2010) in resistance to knee flexion torques associated with greater landing forces (Blackburn and Padua 2009). It is thus evident that lumbopelvic hip complex and knee kinematics that place the center of mass more posterior to the lower extremity subsystem and base of support, such as trunk extension and shallow knee flexion are associated with sagittal plane knee and hip biomechanics that contribute to ACL loading patterns during injury.

Frontal Plane Knee, Hip, and Trunk Biomechanics Associated with Noncontact ACL Injury

Frontal Plane Knee Loads Linked to ACL Loading

In contrast to sagittal plane knee loading mechanisms that are known to directly influence ACL loading via anterior tibial shear force, frontal plane knee loading mechanisms are most notably identified to result in increased ACL loading when combined with sagittal and transverse plane loading patterns (Markolf et al. 1995; Oh, Ashton-Miller, and Wojtys 2011; Withrow, Huston, Wojtys, and Ashton-Miller 2006b; Markolf, Wascher, and Finerman 1993; SHIN, Chaudhari, and Andriacchi 2009; Shimokochi and Shultz 2008). While isolated frontal plane varus and valgus loading of the knee joint has been identified to increase ACL loads, the magnitude of ACL loading that results from isolated frontal plane knee loading is minimal compared to anterior tibial shear force that ensues from sagittal plane biomechanics discussed

above (Withrow, Huston, Wojtys, and Ashton-Miller 2006b; Shimokochi and Shultz 2008; Yu and Garrett 2007). While the magnitude of the frontal plane knee forces that contributes to ACL loading is substantially less compared to sagittal plane knee loads, characteristic frontal plane knee and lumbopelvic hip complex biomechanics have been identified during injury events (Shimokochi and Shultz 2008; Dai et al. 2012; Boden et al. 2010) Furthermore, frontal plane knee (Hewett et al. 2005) and lumbopelvic hip complex biomechanics and neuromuscular control (Zazulak et al. 2007) represent the only known prospective biomechanical risk factors for primary sport-related noncontact ACL injury.

Frontal Plane Knee Biomechanics

Multiple video analysis and retrospective interview studies describe frontal plane knee varus and valgus motion in combination with shallow knee flexion and either internal or external rotation motion during noncontact ACL injury events (Shimokochi and Shultz 2008). It is clear that frontal plane knee varus and valgus motion is a commonly observed component of the noncontact ACL injury event (Shimokochi and Shultz 2008; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a; Yu and Garrett 2007; Krosshaug, Slauterbeck, et al. 2007). However, the exact role frontal plane knee motion plays in ACL loading during injury events is not well understood from observational video or retrospective interview study methodology because it is difficult to determine if the non-physiological frontal plane varus / valgus motion occurring at the knee joint is inciting or consequential relative to ACL rupture (Shimokochi and Shultz 2008; Yu and Garrett 2007; Ali and Rouhi 2010). Frontal plane varus / valgus knee motion reported during noncontact ACL injury events is described as “non-physiological” due to the large estimated magnitudes of frontal knee plane motion falling outside described normal 10° varus / valgus motion allowed at the tibiofemoral articulation prior

to ligamentous strain of the medial collateral ligament (MCL) or the lateral collateral ligament (LCL) when the knee assumes “slight flexion” (McGinty, Irrgang, and Pezzullo 2000; Goodfellow and O'Connor 1978), which is of a magnitude no greater than 30° of flexion, a sagittal plane knee angulation commonly reported during ACL injury events (Shimokochi and Shultz 2008).

During ACL injury events a “valgus collapse” of the knee joint is commonly reported (Shimokochi and Shultz 2008). Valgus collapse events are associated with knee valgus angulations sometimes exceeding 40° during loading in landings that resulted in injury (Boden et al. 2009). Interestingly, varus / valgus angulation values at or temporally proximal to initial contact (4° - 8°) (Boden et al. 2009; Krosshaug, Nakamae, et al. 2007) are rarely reported to exceed the physiological frontal plane joint motion allowed in slight flexion prior to ligamentous stress. Furthermore, varus / valgus angulations within 30 – 50 msec of initial ground contact during injury events have not commonly been reported to exceeded 10° (Boden et al. 2009; Krosshaug, Nakamae, et al. 2007). ACL rupture is estimated to occur within a 30 – 50 msec window following ground contact (Shimokochi and Shultz 2008), thus high-magnitude frontal plane knee motion may occur following ligament failure. While it is difficult to determine if the varus / valgus knee motion observed during injury events directly contributes to ACL loading in-vivo (Ali and Rouhi 2010), in-vitro evaluation of varus / valgus stress concomitantly applied with sagittal and transverse plane loads is reported to significantly contribute to dangerous ACL loading scenarios that may result in ligament failure (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006b; Markolf, Wascher, and Finerman 1993). Additionally, frontal plane knee kinematics and kinetics have been described to predict ACL injury risk in female adolescent athletes (Hewett et al. 2005). Thus frontal plane knee biomechanics are associated

with ACL injury events, loading mechanisms, and injury risk and warrant consideration for evaluation in studies aimed at understanding and preventing noncontact sport-related ACL injury.

The results of observational analysis of injury events implicate a multi-planar nature of the noncontact ACL injury mechanism, directing in-vitro and in-vivo study methodology to evaluate the effects of combined multi-planar knee loading on ACL loading (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007). As observational reports describe a knee extension or hyperextension mechanism to be associated with injury, inducing anterior tibial shear force at the knee joint, in-vitro and in-vivo evaluations commonly combine a anterior tibial shear force, quadriceps force, knee extension moment, or a weight-bearing load with a frontal plane torque at the knee to simulate estimated loading scenarios during injury events (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007). Interestingly, in contrast to injury events that are observed to incorporate weight bearing when the quadriceps musculature is active, a combined quadriceps and varus or valgus load applied to the knee at less than 40° of knee flexion resulted in decreased ACL strain (Arms et al. 1984). Furthermore, Fleming et al.'s. 2001 in-vivo report of combined weight-bearing and varus or valgus load application did not observe an increase in ACL loading when compared to weight-bearing in isolation (Fleming et al. 2001). It is possible frontal plane varus or valgus load during weight bearing and high-magnitude quadriceps force production does not substantially influence ACL loading, and that sagittal plane factors such as anterior tibial shear force dominate ACL loading parameters during injury events (Shimokochi and Shultz 2008; Yu and Garrett 2007; Dai et al. 2012).

Alternatively, McLean et al. simulated the isolated effects of sagittal plane knee loads during a sidestep cutting task, and observed that anterior tibial shear force from sagittal plane

loading alone is not sufficient to produce ACL loading conditions that would result in ligament rupture during side-step cutting (S. G. McLean et al. 2004). McLean et al. concluded frontal plane factors should not be ignored and considered responsible for inducing dangerous loading conditions at the knee during sidestep cutting tasks, an identified mechanism of sport-related noncontact ACL injury (Shultz et al. 2012). Although McLean et al's. results may have limited validity due to the inherent systematic error in modeling and simulation study methodology (Ali and Rouhi 2010), they should not be ignored. McLean et al's methodology evaluated knee loads during an athletic task that may more accurately represent human motion and resultant joint loading during athletic activity compared to in-vitro cadaver study methods that evaluate ACL loading in relatively controlled environments and don't account for in-vivo neuromuscular control across the knee joint (Shimokochi and Shultz 2008). Thus, further discussion of combined sagittal-frontal plane knee loading is warranted and has been supported by other in-vitro cadaveric studies (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006b; Markolf et al. 1990).

Markolf et al. evaluated the combined effects of anterior tibial shear force and varus or valgus loading of the knee joint from -10° (hyperextension) - 90° flexion (Markolf et al. 1995). From hyperextension to 20° of knee flexion Markolf et al. observed that the addition of either a varus or valgus torque increased ACL loading (Markolf et al. 1995). Beyond 30° of flexion the addition of a valgus torque resulted in continued elevations in ACL strain compared to isolated anterior tibial shear force (Markolf et al. 1995). Berns et al. observed similar results in which anterior tibial shear force and valgus torque applied in combination resulted in an additive ACL loading effect versus anterior tibial shear force alone, but did not observe an additive effect of varus torque (Berns, Hull, and Patterson 1992). Markolf et al. also applied an internal rotation

torque in addition to anterior tibial shear force and noted the greatest strain compared to combinations of multi-planar loading (Markolf et al. 1995). While Markolf et al.'s finding regarding dangerous loading of the ACL when anterior tibial shear force is combined with internal rotation torque is important, numerous accounts report the tibia to externally rotate relative to the femur during noncontact ACL injury events (Ireland 1999; Shultz et al. 2012; Shimokochi and Shultz 2008). Furthermore, Markolf et al. observed tibial external rotation in addition to anterior tibial shear force to decrease ACL strain throughout the knee flexion range of motion (Markolf et al. 1995). While transverse plane knee biomechanics should not be ignored when evaluating ACL injury mechanics, transverse plane motion of the tibia relative to the femur is difficult to quantify from video analysis due to limited image resolution (Ali and Rouhi 2010) and biomechanical analysis due to the limited motion about the longitudinal axis and substantial motion artifact (Kristianslund, Krosshaug, and van den Bogert 2012; Ali and Rouhi 2010). In further support of the additive influence of a frontal plane loading, Withrow et al. simulated single-leg drop landings to evaluate the combined effects of impulsive compressive forces, external flexion moment, and external valgus moment applied in-vitro to a cadaveric knee joint initially positioned at 25° flexion (Withrow, Huston, Wojtys, and Ashton-Miller 2006b). Pre-tensioned steel cables attached at the patellar tendon, medial and lateral hamstrings, and gastrocnemius insertions were used to simulate muscle forces action across the knee joint prior to impulsive force application. Withrow et al. observed that the addition of an impulsive external valgus moment induced a simulated ground reaction force vector applied 4 cm posterior to the knee joint axis of rotation (to produce external flexion moment) and 15° lateral to the knee's sagittal plane increased ACL loading compared to when the ground reaction force vector was applied neutral to the knee's sagittal plane (Withrow, Huston, Wojtys, and Ashton-Miller

2006b). Withrow et al's. methodology represents an impulsive multi-planar loading scenario that is characteristic of injury events that includes the application of an off-plane and off-axis ground reaction force vector to the lower extremity sub-system with simulated muscle forces (Shimokochi and Shultz 2008; Krosshaug, Nakamae, et al. 2007; Koga et al. 2010). Withrow et al's. results provide insight regarding frontal plane knee biomechanics that may be protective against ACL loading in-vivo during similar loading scenarios. neuromuscular control strategies that limit frontal plane knee loading may limit the potential for ACL rupture during exposure to impulsive landing activities with the off-sagittal plane ground reaction force exposure.

Collectively, in-vivo and in-vitro loading studies suggest that single-plane loading scenarios limit ACL strain, while there is an additive effect of varus / valgus and internal rotation torques to simulated high-magnitude anterior tibial shear force that results from quadriceps force applied at shallow knee flexion angles and compressive loading that is associated with weight bearing activity (Shimokochi and Shultz 2008; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a). Thus it can be elucidated that the injury mechanism is multi-planar in nature, and should not be isolated to a single plane in future analyses.

Neuromuscular control strategies implemented during athletic activities such as jump-landings, stop-jumps, drop-landings, single-leg landings, cutting and hopping tasks have been targeted for prospective biomechanical evaluation and modeling studies in effort to identify noncontact ACL injury biomechanical risk factors present in individuals prior to an injury event during their athletic career and sport participation (Ali and Rouhi 2010). To date, a single prospective biomechanical risk factor study has identified frontal plane knee biomechanics to be predictive of injury in a sample (n= 205) of female adolescent soccer, basketball, and volleyball athletes (Hewett et al. 2005). During Hewett et al's. prospective study, nine ACL injuries

occurred over the course of the three-season study period. Female athletes who went on to sustain ACL injury (n= 9) were identified to exhibit significantly greater peak knee valgus angulation and experience almost 2.5 times greater external knee valgus moment during the landing phase of a drop-jump landing compared to their uninjured counterparts (Hewett et al. 2005). Injured athletes also exhibited less peak knee flexion angle and 20% greater vertical ground reaction forces compared to the uninjured cohort which may have increased frontal plane loading demands (Hewett et al. 2005). Although Hewett et al.'s results implicate a multi-planar injury risk profile, the study results should be interpreted with caution, as the low number of injuries limits the generalizability of the study findings. Furthermore, the external knee valgus moment and ground reaction force data are not normalized to individual participants' anthropometrics and may limit the predictive validity of the kinetic data from this study. While the study methodology and data present limitations, the results of Hewett et al.'s study suggest that greater maximal knee valgus motion and external moment are frontal plane knee biomechanics linked to ACL injury with a limited predictive capacity in adolescent female athletes.

Frontal plane knee biomechanics are associated with noncontact ACL injury events, mechanical loading patterns, and prospective injury risk. Specifically, medial knee collapse or valgus collapse is commonly observable during injury events (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a), however the temporal relationship of the medial collapse pattern to timing of ligament rupture is not well understood. In addition to valgus collapse, there is some evidence that varus motion at the knee joint occurs prior to valgus collapse and may precede injury during some single-leg landing activities (Olsen et al. 2004). While the exact frontal plane knee

biomechanics of ACL injury mechanisms remain elusive at the time of writing, it is clear that both varus and valgus loading contribute to ACL strain when combined with anterior tibial shear forces and impulsive compressive loads at shallow knee flexion angles commonly observed during ACL injury events (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a). Frontal plane biomechanics demonstrate some utility as identified prospective risk factors for ACL injury in adolescent female athletes, implicating greater knee valgus tendency (angle and external moment) may increase an individual's risk for subsequent ACL injury (Hewett et al. 2005). Thus, future methodology should realize frontal plane knee angle and moment as important variables to consider in continued effort to understand and prevent sport-related noncontact ACL injury.

Frontal Plane Lumbopelvic Hip Complex Biomechanics

The frontal plane lumbopelvic hip complex link between the lower extremity sub-system and whole body center of mass behaves similarly to the previously discussed sagittal plane lower extremity-lumbopelvic hip complex link (Powers 2010; Mendiguchia et al. 2011). Video analyses have described lumbopelvic hip complex biomechanics during ACL injury events, however a consistent biomechanical pattern similar to “greater hip flexion with an extended trunk” is not reported for frontal plane lumbopelvic hip complex (Krosshaug, Slauterbeck, et al. 2007; Boden et al. 2009). The range of frontal plane hip motion during ACL injury events varies from 7° of adduction to 48° of hip abduction (Krosshaug, Nakamae, et al. 2007; Hewett, Torg, and Boden 2009; Boden et al. 2009). While a substantial amount of variability in frontal plane hip angle is reported during injury events Boden et al. 2009 observed a mean difference of 3.7 ±11.7° greater hip abduction in injured participants versus matched controls during video

analysis of injury events (Boden et al. 2009). Greater hip abduction may be characterized as a laterally “outstretched” hip during injury events (Boden et al. 2009; Hewett, Torg, and Boden 2009). In contrast to the variability in frontal plane hip positioning observed during injury events, lateral trunk flexion atop the injured limb appears to be more consistently identified during noncontact ACL injury events, and is associated with an observed dynamic knee valgus motion, and eventual valgus collapse (Hewett, Torg, and Boden 2009). In a comparison of ACL injured male and female athletes matched to uninjured controls performing similar activities, Hewett et al. observed a trend in greater lateral trunk flexion between athletes who sustained ACL injury ($11.1 \pm 1.2^\circ$) and uninjured controls ($4.2 \pm 9.6^\circ$) female athletes (Hewett, Torg, and Boden 2009). While video analyses of frontal plane lumbopelvic hip complex do not consistently identify a frontal plane biomechanical pattern associated with noncontact ACL injury, there is some observational support that lateral trunk flexion on a laterally outstretch hip may be associated with an ACL injury mechanism (Hewett and Myer 2011; Hewett, Torg, and Boden 2009; Boden et al. 2009).

Although a consistent frontal plane lumbopelvic hip complex biomechanical profile is not readily identified during ACL injury events, frontal plane trunk neuromuscular control is a prospective risk factor for ACL injury in collegiate athletes (Zazulak et al. 2007). In 2007 Zazulak et al. prospectively assessed trunk neuromuscular control as a measure of trunk displacement after sudden force release from an isometric resistance against 30% maximal isometric force exertion from the anterior, posterior, and lateral directions (Zazulak et al. 2007). Zazulak et al. quantified trunk angular displacement in the directions of forward flexion, extension, and lateral bending (lateral flexion). Lateral trunk flexion at 150 msec following sudden force release and maximal lateral trunk displacement were significantly greater in the AC

-injured cohort (n= 6) (Zazulak et al. 2007). The results of Zazulak et al's. study were entered into a binary logistic regression model to predict knee injury risk. Lateral trunk flexion was the strongest predictor of ACL injury risk, with individuals who exhibited greater lateral trunk flexion having 2.32 the odds of sustaining ACL injury (Zazulak et al. 2007). While Zazulak et al's. findings are novel and provide further understanding regarding the association between ACL injury risk and lumbopelvic hip complex neuromuscular control, they are not without limitations. One primary limitation of Zazulak et al's. study is the small number of observed ACL injuries limiting the power of the regression model to predict ACL injury specifically, as the binary logistic regression model was powered to predict non-specific knee injury (based on 21 knee injuries to achieve a power of 0.8) (Zazulak et al. 2007). Furthermore, there is no report of predictor variable coefficient estimates, thus it is difficult to estimate the increase in odds of ACL injury per unit increase in lateral trunk flexion displacement (Zazulak et al. 2007). Although, Zazulak et al's results present with limitations, they identify lateral trunk neuromuscular control, specifically larger lateral trunk displacements as a prospective risk factor for ACL injury.

The results of Zazulak et al's prospective risk factor study and reports of frontal plane lumbopelvic hip complex motion during sport-related noncontact ACL injury events has prompted evaluation of the influence of frontal plane lumbopelvic hip complex biomechanics on knee biomechanics associated with noncontact ACL injury (Ali and Rouhi 2010; Jamison, Pan, and Chaudhari 2012; Powers and Fisher 2010; Mendiguchia et al. 2011; Hewett and Myer 2011). Evidence suggests that frontal plane lumbopelvic hip complex biomechanics and neuromuscular control influence knee biomechanics (Hollman et al. 2014; Hollman et al. 2009; Willson 2007; Willson and Davis 2008). Furthermore, hip adduction is identified to be the primary contributor

to dynamic knee valgus motion or medial knee displacement, as a linear medial displacement of the distal femur occurs with hip adduction rotation (Hollman et al. 2009; Willson and Davis 2008). A medial displacement of the femoral condyles secondary to frontal plane hip adduction, positions the proximal articular surface of the tibiofemoral joint medial to the foot, or the base of support during single-leg athletic activity (Hollman et al. 2009; Hollman et al. 2014; Hollman et al. 2012).

As described in the section above regarding the influence of the center of mass location relative to the base of support and knee joint on sagittal plane knee loading, a similar influence is present in the frontal plane. The ability of the ground reaction force vector to exert external moment about the knee joint in the frontal plane is dictated by the orientation of the ground reaction force vector within the frontal plane relative to the knee joint's anterior-posterior axis of rotation, about which varus / valgus rotation occurs (Winter 2009; Powers 2010; Hewett et al. 2005; Frank et al. 2013; Jamison, Pan, and Chaudhari 2012; Houck, Duncan, and De Haven 2006). The frontal plane orientation of the ground reaction force vector is dictated by the position of the center of mass relative to the base of support or the center of pressure location from which the ground reaction force vector originates to act on or interface with the kinetic chain at the foot segment (Winter 2009). When the ground reaction force vector is oriented relatively in-line with the anterior-posterior axis of the knee joint, the ground reaction force vector has no relative varus / valgus moment influence about the knee. However, when the ground reaction force vector is oriented medially to the knee joint anterior-posterior axis the ground reaction force vector exerts an external varus torque about the knee (Winter 2009; Powers 2010). Alternatively, lateral trunk lean orients the ground reaction force vector laterally to the knee joint's anterior-posterior axis of rotation and exerts external valgus torque which promotes

knee valgus angulation if not met with appropriate internal knee varus moment resistance (Jamison, Pan, and Chaudhari 2012; Winter 2009; Houck, Duncan, and De Haven 2006; Powers and Fisher 2010; Hewett and Myer 2011).

The influence of lateral frontal plane trunk angulation on subsequent lateral center of mass deviation and resultant ground reaction force vector orientation relative to the knee joint is further supported by empirical biomechanical studies (Jamison, Pan, and Chaudhari 2012; Houck, Duncan, and De Haven 2006; Dempsey et al. 2009). Lateral trunk flexion has been consistently identified to be associated with greater external knee valgus (internal knee varus) loading of the knee joint during single-limb activities such as side-step cutting which requires a sagittal plane knee extension breaking force as well as a frontal plane acceleration of the center of mass in the new direction of travel (Jamison, Pan, and Chaudhari 2012; Houck, Duncan, and De Haven 2006; Frank et al. 2013; Dempsey et al. 2009). Thus it appears that lateral trunk lean during side-step cutting or single-leg acceleration-deceleration tasks has the potential to increase frontal plane knee loading during the application of a sagittal plane knee extension breaking force, representing a condition of combined sagittal-frontal plane loading that is reported to result in increased ACL loading in-vitro (Markolf et al. 1995; Withrow, Huston, Wojtys, and Ashton-Miller 2006b).

Aberrations in neuromuscular control of the lumbopelvic hip complex further contribute to frontal plane knee loading mechanics via an observed relationship between limited hip muscle abduction strength and a “compensatory Trendelenburg” movement pattern, in which an individual elevates their contralateral (non-support) pelvis and laterally flexes the trunk to effectively orient the ground reaction force vector in-line with the hip joint’s anterior-posterior axis of rotation, minimizing internal hip abduction moment demand (Neumann 2010; Lawrence

et al. 2008; Powers and Fisher 2010). Consequently the ground reaction force is oriented lateral to the knee joint frontal plane axis of rotation, increasing external valgus (internal varus) moment frontal plane loading at the knee joint (Neumann 2010; Lawrence et al. 2008; Powers and Fisher 2010).

Summary of Frontal Plane Knee and lumbopelvic hip complex Biomechanics Associated with Sport-Related Noncontact ACL Injury

The results of this review identify frontal plane knee, hip, and trunk biomechanics to be associated with sport-related noncontact ACL injury via either mechanistic or risk factor interpretations (Shimokochi and Shultz 2008; Dai et al. 2012; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009b; Hewett and Myer 2011; Boden et al. 2010). Video analysis data describe knee valgus and varus motion occurring during injury events, however the contribution of varus and valgus loading to ligament rupture in-vivo during injury events remains debated (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007). Regardless of the in-vivo loading contribution from frontal plane torques about the knee joint during injury events, in-vitro evidence suggests frontal plane moments alone are not sufficient to result in ACL injury (Shimokochi and Shultz 2008; Yu and Garrett 2007; Dai et al. 2012). However, when applied in combination with sagittal plane loads such as anterior tibial shear force at shallow knee flexion angles, frontal plane knee moments significantly elevate ACL loads in-vitro (Shimokochi and Shultz 2008; Yu and Garrett 2007; Dai et al. 2012). Additionally, there is low-level evidence peak knee valgus angle and moments are predictive of ACL injury risk in an adolescent female athlete population (Hewett et al. 2005). While frontal plane knee biomechanics represent noncontact ACL injury risk factors, mechanisms, and are observable during injury events that are fundamentally influenced by lumbopelvic hip complex

biomechanics (Powers 2010). Lateral deviation of the whole body center of mass relative to the knee joint during athletic motions appears to substantially contribute to prevalence of frontal plane knee valgus tendency secondary to compensatory patterns for limited hip abduction neuromuscular control (Hollman et al. 2014; Hollman et al. 2009; Willson 2007; Willson and Davis 2008). Thus, there is a considerable interaction between frontal plane lumbopelvic hip complex neuromuscular control and knee biomechanics associated with ACL injury. The results of this review implicate frontal plane knee and lumbopelvic hip complex biomechanics should be included in investigation of neuromuscular control patterns aimed at understanding and preventing sport-related noncontact ACL injury.

ACL Injury Biomechanics Summary and their Proposed Influence on Sport-Related Noncontact ACL Injury in a High-Risk Athlete Population

While this review extensively described the association between sagittal and frontal plane knee and lumbopelvic hip complex biomechanics with sport-related noncontact ACL injury risk, loading mechanisms, and injury biomechanics, the discussion is not exhaustive. In addition to frontal and sagittal plane knee and lumbopelvic hip complex biomechanics, ankle and foot biomechanics have also been described to be associated with ACL injury (Shimokochi and Shultz 2008; Boden et al. 2010). Furthermore, transverse plane biomechanics at the hip and knee such as hip internal rotation and knee external rotation have been observed during injury events (Shimokochi and Shultz 2008; Dai et al. 2012). While a in-depth discussion of lower extremity transverse plane and ankle-biomechanics are not provided by this review, a focus on frontal and sagittal plane knee and lumbopelvic hip complex biomechanics is supported by recent evaluations of initial impact phase energy absorptions, frontal and sagittal plane knee and lumbopelvic hip complex biomechanics by Norcross et al. during double-leg jump landings

(Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013b; Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013a). Norcross et al. observed greater initial impact phase sagittal and frontal plane energy absorption to be associated with biomechanics associated with ACL injury such as greater anterior tibial shear force, internal knee extension and varus moments, vertical ground reaction forces, knee valgus, and hip adduction motion (Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013b; Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013a). High initial impact phase energy absorption is associated with rapid ACL loading during the initial phase of ground contact when ACL rupture is described to occur during injury mechanisms (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007).

Collectively, review of the literature implicates that frontal and sagittal plane knee and lumbopelvic hip complex biomechanics represent factors that influence ACL loading, noncontact injury mechanisms, and prospective noncontact risk factors (Dai et al. 2012; Yu and Garrett 2007; Shimokochi and Shultz 2008). Specifically, anterior tibial shear force appears to be a primary ACL loading mechanism, and likely represents a significant element of the injury mechanism. Consensus identifies a shallow ($<30^{\circ}$ - 40°) knee flexion angle to influence anterior tibial shear force, with an extended knee posture reported during injury events (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007). Epidemiological studies identify shallow knee flexion posture and reduced peak knee flexion angles during landings as prospective risk factors for ACL injury (Hewett et al. 2005). Furthermore, a high-magnitude quadriceps force applied at a shallow knee flexion angle is necessary to generate sufficient internal knee extension breaking moment. However, a high-magnitude quadriceps force applied at a shallow knee flexion angle contributes to high anterior tibial shear force values (Shimokochi and Shultz 2008;

Dai et al. 2012; Yu and Garrett 2007). Elicitation of high-magnitude quadriceps force to generate internal knee extension moment during energy absorption is associated with sagittal plane lumbopelvic hip complex biomechanics that are observed during injury events (Sheehan, Sipprell, and Boden 2012; Blackburn and Padua 2009).

Sagittal plane lumbopelvic hip complex biomechanics that position the whole-body center of mass posterior to the knee joint or base of support increase landing forces, elevate quadriceps activity, decrease knee flexion angles, increase knee extension moments, magnifying anterior tibial shear force and the potential for ACL loading during athletic motion (Sheehan, Sipprell, and Boden 2012; Blackburn and Padua 2009; Kulas, Hortobágyi, and DeVita 2010; Kulas, Hortobágyi, and DeVita 2012). Trunk flexion combined with hip and knee flexion appears to be a movement strategy that may be associated with decreased noncontact ACL injury risk and loading mechanics, representing an optimal sagittal plane energy absorption strategy. Thus, lumbopelvic hip complex biomechanics that position the center of mass posterior to the knee joint with a concomitant shallow knee flexion angle represents a movement profile that is linked to sport-related noncontact ACL injury.

While sagittal plane biomechanics exhibit a direct link to noncontact ACL injury risk, loading, and injury events, frontal plane knee and lumbopelvic hip complex biomechanics advance the definition of a movement profile associated with sport-related noncontact ACL injury. Isolated frontal plane knee varus / valgus loads are not consistently described to induce ACL loading sufficient to result in ligament injury, however when varus or valgus loads are combined with anterior tibial shear force they can substantially increase ligament strain (Shimokochi and Shultz 2008; Dai et al. 2012; Yu and Garrett 2007). In addition, accessory frontal plane knee motions occurring in conjunction with sagittal plane biomechanics that

contribute to anterior tibial shear force are commonly reported during noncontact ACL injury events, suggesting frontal plane knee varus and valgus loads may contribute to ACL loading during injury events (Krosshaug, Nakamae, et al. 2007; Koga et al. 2010). Furthermore, prospective epidemiological evidence identifies greater initial contact and peak knee valgus angle to be predictive of ACL injury (Hewett et al. 2005).

Interestingly, both knee varus and valgus loads and angles are described to contribute to ACL loading and excessive frontal plane knee motions are observed during injury events, however the specific direction of frontal plane knee motion (varus or valgus) associated with noncontact ACL injury risk remains elusive (COCHRANE et al. 2007). Collectively, increased knee varus / valgus angles and moments represent variables that contribute to off-sagittal plane energy absorption (Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013a). Thus, biomechanics promoting knee varus or valgus angles and moments are minimal in a safe and effective energy attenuation strategy, maximizing sagittal plane energy absorption (Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013a; Yu and Garrett 2007).

Frontal plane lumbopelvic hip complex biomechanics are associated with frontal plane knee biomechanics. A lateral deviation of the whole-body center of mass relative to the knee joint achieved via lateral trunk flexion angle is associated with increased knee valgus biomechanics and mitigation of internal hip abduction moment generation, lending to a greater propensity toward hip adduction angulation (Jamison, Pan, and Chaudhari 2012; Houck, Duncan, and De Haven 2006; Dempsey et al. 2012). Decreases in hip abduction moment generation and increased hip adduction motion (Houck, Duncan, and De Haven 2006) likely contribute to increased frontal plane knee motion, and may represent key elements contributing to the “valgus collapse” described during injury events, with lateral trunk flexion commonly being observed

during injury events (Hewett, Torg, and Boden 2009). Mechanistically, a lateral displacement of the whole-body center of mass positions the ground reaction force vector laterally to the knee joint, increasing the ground reaction force's influence on frontal plane knee moment, contributing to elevated multi-planar knee loading (Jamison, Pan, and Chaudhari 2012; Frank et al. 2013). Frontal plane lumbopelvic hip complex biomechanics appear to be associated with ACL loading mechanisms and injury events, but also represent prospective risk factors for injury. Excessive lateral trunk flexion displacements are predictive of ACL injury in collegiate athletes (Zazulak et al. 2007). Individuals with excessive frontal plane knee motion, tendency toward hip adduction, and excessive lateral trunk motion during athletic tasks may represent a population with a biomechanical profile associated with ACL injury.

Athletes with limited knee, trunk, and hip flexion, excessive lateral trunk motion, a disposition toward hip adduction, and increased frontal plane knee motion during athletic tasks represent a population with a movement profile linked to noncontact ACL injury. Individuals with a kinematic profile associated with noncontact ACL injury may exhibit neuromuscular control strategies that influence load attenuation or energy absorption that increases biomechanical demand on the body (Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013b; Norcross, Lewek, Padua, Shultz, Weinhold, and Blackburn 2013a). Persons exhibiting a movement profile associated with increased biomechanical demand may be exposed to greater physiological demand and tissue stress compared to individuals who do not exhibit a movement profile linked to noncontact ACL injury (Franklyn-Miller et al. 2014). Evaluating the impact of a movement profile associated with noncontact ACL injury on biomechanical and physiological demand in a population at high risk for injury may provide insight regarding factors that underlie sport-related ACL injury.

Female college-aged field and court sport athletes represent a population at high risk for sustaining noncontact ACL injury (Hootman, Dick, and Agel 2007; Beynnon et al. 2014). While ACL injury incidence is relatively high in female college-aged soccer, basketball, lacrosse, rugby and team handball athletes compared to their male counterparts participating similar sports and female athletes participating in other sports, the incidence of injury of female college-aged athletes in the aforementioned sports is generally less than 1 injury per 1,000 player exposures (Hootman, Dick, and Agel 2007; Beynnon et al. 2014). Thus there is a substantial fraction of the female college-aged soccer, basketball, lacrosse, rugby and team handball athlete population who do not go on to suffer a noncontact ACL injury. These uninjured individuals may possess inherent biomechanical and physiological characteristics that limit their risk of noncontact ACL injury during sport participation. Investigating differences between individuals who exhibit a movement profile associated with ACL injury and those who do not in a high-risk female athlete population may explain underlying factors that drive an increased susceptibility for noncontact ACL injury.

Clinical Identification of a Movement Profile Associated with Sport-Related Noncontact ACL Injury

Identification of a movement profile associated with noncontact ACL injury inclusive of limited knee, trunk, and hip flexion, lateral trunk motion, a disposition toward hip adduction, and increased frontal plane knee motion during athletic tasks is possible through complex 3 – dimensional (3D) motion capture. However, 3D motion analysis techniques are time consuming, complex, costly, and unrealistic in many clinical settings. The literature describes a multitude of clinically oriented movement assessments that are used to evaluate an athlete's musculoskeletal

injury risk (Dallinga, Benjaminse, and Lemmink 2012; Teyhen et al. 2014). The assessments commonly take the form of evaluating an individual's performance during an functional movement, athletic, and/or balancing task (Dallinga, Benjaminse, and Lemmink 2012; Teyhen et al. 2014). Some evaluations evaluate continuous performance variables such as “reach distance” during the Y-Balance assessment, whereas other assessments instruct the clinician to identify movement “compensations” or “errors” during observation of the functional or athletic task as in the Functional Movement Screen or The Landing Error Scoring System to tally a total assessment score (Dallinga, Benjaminse, and Lemmink 2012; Teyhen et al. 2014).

To date, clinical movement assessments appear to demonstrate high variability in their validity, sensitivity, specificity, reliability, and predictive capacity to prospectively identify individuals who go on to suffer a musculoskeletal injury (Teyhen et al. 2014; Dallinga, Benjaminse, and Lemmink 2012). While some clinical assessments demonstrate moderate to excellent levels of sensitivity, specificity, and reliability regarding prediction of nonspecific musculoskeletal or a particular diagnosis, no clinical screening tool currently exists that repeatedly predicts sport-related noncontact ACL injury with high levels of specificity and sensitivity (Dallinga, Benjaminse, and Lemmink 2012; Teyhen et al. 2014).

No current clinical assessments demonstrate excellent predictive capacity for sport-related noncontact ACL injury. However, The Landing Error Scoring System (LESS) is a valid global movement assessment tool that can easily be employed by clinicians to identify individuals whom exhibit biomechanics associated with sport-related noncontact ACL injury (Teyhen et al. 2014; Padua et al. 2009). The LESS exemplifies a clinical screening tool that requires minimal resources, thus can be economically deployed across a range of clinical settings. The LESS protocol is detailed by Padua et al. 2009. The LESS requires the use of two

“off-the-shelf” video recording devices and a stable platform 30 cm in height (figure 3.3). To establish the testing area format, a line or landing target zone is placed on the floor. The two video recording devices are positioned approximately 1.5 m anterior (1) and to the right (1) of the landing target line arranged with their optical axes forming a perpendicular converging at the landing target line. The 30 cm box is positioned posterior to the landing target line at a distance of 50% the test subject’s height. For the testing procedure, the subject is instructed to step up onto the box, face forward, and *“jump down forward of the line, and rebound upward for a maximal vertical jump”* (Padua et al. 2009). The test subject performs 3-5 jump trials which are recorded on video and then scored by the clinician following the jump-landing protocol (Padua et al. 2009).

The utility of the LESS in its capacity to identify individuals whom exhibit biomechanics associated with sport-related noncontact ACL injury was validated in a 2009 report by Padua et al. Padua et al. deployed the LESS in population of 2,691 subjects (males:1655, females: 1036) while simultaneously evaluating 3D kinematics and ground reaction forces at initial ground contact and during the stance phase of the jump-landing (Padua et al. 2009). Thus, Padua et al.’s methodology accomplished simultaneous LESS scoring and 3D biomechanical analysis of each study participant. A single rater scored a subsample of 25 male and 25 female participants video data on two separate occasions to establish intrarater reliability. A second rater who was blinded to the first rater’s scoring results, scored the subsample’s video data to establish interrater reliability. The LESS was reported to have good interrater (0.84) and excellent intrarater (0.91) reliability (Padua et al. 2009). Furthermore, the LESS exhibited standard errors <1 for both interrater and intrarater reliability, identifying the LESS to be a sensitive clinical assessment of jump-landing biomechanics (Padua et al. 2009).

To further evaluate the validity of the LESS's capacity to predict 3D biomechanics from the 17-item clinical scoring criteria, Padua et al. divided the sample based on LESS scores into quartiles, representing *Excellent* (≤ 4), *Good* (>4 to ≤ 5), *Moderate* (>5 to ≤ 6), *Poor* (>6) movement profiles (Padua et al. 2009). Multiple 3D biomechanical differences were observed between all groups (Padua et al. 2009). Most notably, a *poor* movement profile was associated with significantly limited knee and hip flexion motion, greater frontal plane knee valgus motion, higher internal knee extension and knee valgus moments, and higher vertical ground reaction and anterior tibial shear forces compared to 3D biomechanics observed in the *excellent* movement profile quartile (Padua et al. 2009). The results of Padua et al.'s study suggest that individuals who score *poor* on the LESS exhibit a biomechanical profile associated with ACL loading, noncontact ACL injury mechanisms and / or movement patterns observed during injury events, and prospective biomechanical risk factors for sport-related noncontact ACL injury (Dai et al. 2012; Yu and Garrett 2007; Shimokochi and Shultz 2008). While the LESS may not demonstrate a consistent capacity to predict sport-related noncontact ACL injury, the LESS represents a valid and reliable clinical tool able to discriminate between individuals who demonstrate biomechanics associated with sport-related noncontact ACL injury (*poor*) and individuals who do not (*excellent*) exhibit a biomechanical profile associated with injury (Dai et al. 2012; Yu and Garrett 2007; Shimokochi and Shultz 2008).

Poor Movement as an Underlying Factor Associated with Noncontact ACL Injury During Sport Participation in a High-Risk Population The female college-aged field and court sport athlete who exhibits a *poor* movement profile represents a particular population hypothesized to be at substantially high risk for suffering a sport-related noncontact ACL injury. However, the

underlying physiological mechanisms responsible for driving a high sport-related noncontact ACL injury risk remain elusive. Complex interacting physiological factors respond to high-intensity exercise exposure during sport (Knicker et al. 2011). During exposures to high training loads athletes experience elevated levels of surrogate markers of peripheral and central fatigue (Foster et al. 2001; Foster 1998). Interestingly, there is substantial variability between individuals' fatigue responses when exposed to a similar exercise stimulus (Foster et al. 2001; Wallace, Slattery, and Coutts 2014).

Poor biomechanics are associated with higher biomechanical demand, and may induce an exacerbated exercise-induced fatigue response during sport participation (Di Michele and Merni 2014; McCann and Higginson 2008; Dicharry 2010). Exercise-induced fatigue exposure provokes biomechanics associated with noncontact ACL injury in healthy female athletes without regard to their movement profile (Santamaria and Webster 2010; S. G. McLean and Samorezov 2009; B. D. McLean, Petrucelli, and Coyle 2012; Benjaminse et al. 2008; S. G. McLean et al. 2007). To date, no study methodology has evaluated the impact of a *poor* movement profile associated with noncontact ACL injury on an individual's biomechanical and physiological response to high-intensity exercise-induced fatigue in a demographic with a high sport-related noncontact ACL injury risk. We hypothesize that athletes with *poor* movement profiles experience significantly greater biomechanical and physiological demands when participating in field and court sports compared to athletes with *excellent* movement profiles. Differences between *poor* and *excellent* movement profiles within the high-risk female athlete population may influence disparity in biomechanical, biochemical, physical, and psychological responses to high-intensity exercise-induced fatigue; representing underlying factors contributing to an elevated risk for sustaining noncontact ACL injury during sport participation.

SECTION THREE: The Proposed Interaction Between Movement Profile and Total-Body Physiological Response to High-Intensity Exercise-Induced Fatigue

The aim of the following literature review is to describe the underlying mechanisms responsible for high-intensity exercise-induced fatigue to further the understanding of the influence of fatigue on biomechanics associated with sport-related noncontact ACL injury. While numerous studies have observed fatigue exposure to incite biomechanics associated with noncontact ACL injury, no study to date has evaluated the influence of an individual's movement profile on their fatigue response to high-intensity exercise exposure. The following review will provide rationale to implicate movement as a modifier of an individual's biomechanical, biochemical, and physical markers of fatigue in response to high-intensity exercise.

Exercise-Induced Fatigue is an Interactive Process that Influences Muscle Function

A exercise-induced fatigue state ensues when physical activity demand exceeds the current physical capacity of the system (Knicker et al. 2011; J. M. Davis 1995; Robson-Ansley, Gleeson, and Ansley 2009). As physical capacity is exceeded, system efficiency is compromised, and commonly manifests as decreased performance (Knicker et al. 2011; Noakes 2000). During physical activity, system bioenergetic pathways operate to provide energy substrates to working muscle tissue to permit muscular contraction. Ultimately, two primary factors determine effective skeletal muscle force output and ultimately power (Knicker et al. 2011; J. M. Davis 1995; Noakes 2000); neurological drive to the muscle and adenosine triphosphate (ATP) turnover (Robergs, Ghiasvand, and Parker 2004; Cairns et al. 2005; Knicker et al. 2011; J. M. Davis 1995). When there is a decrease in neurological drive or available ATP to the muscle a

decrease in muscular performance ensues. Thus, there are both *peripheral* (metabolic / energy substrate availability-related) and *central* (neurological drive-related) factors that mediate skeletal muscle performance during physical activity.

The effective action of skeletal muscle can be described at the muscle performance (contraction properties), skill/task/athletic performance (as in running), and competition or training performance (such as sport competition) levels (Knicker et al. 2011). *Muscular performance* is the most basic element of athletic performance, defined as the strength and velocity of muscular contraction defining muscular power (Knicker et al. 2011). Isolating fatigue effects to the *muscular performance* level reveals declines in contraction force and velocity that owe to technique deviation, such as recruitment of synergistic muscles in order to maintain motor skill performance and subsequent athletic performance to sustain high levels of competition or exercise performance (Gabbett and Jenkins 2011; Noakes 2000; Knicker et al. 2011; Rahnama et al. 2003). *Athletic/skill/task performance* describes the resultant incorporation of muscular force output across a joint (or multiple joints) to achieve a certain posturing (dynamic) stability) or motion that contributes to a task or skill such as running, sprinting, jumping, or throwing (Knicker et al. 2011). In regards to *competition* or *exercise performance* in sport, the effects of fatigue are readily apparent, the individual experiencing fatigue begins to reveal observable decrements in effective decision-making, complex motor skill execution, and athletic performance variables such as speed, acceleration, and agility (Robson-Ansley, Gleeson, and Ansley 2009; Noakes 2000).

Although the effective action of skeletal muscle can be described as a simple contraction or relaxation, the primary goal of systemic physiology during physical activity is to optimize skeletal muscle function (brooks, fahey, and baldwin 2004). Ultimately, field and court-sport

participation demands the combination and integration of power and endurance activity, with workloads ranging from short bursts of high power output, as in sprinting, to periods of moderate speed, lower-intensity running or jogging (Knicker et al. 2011; Cairns et al. 2005). Although field and court-sport participation incorporates some periods of seemingly moderate to low workloads, the total physiological stress imposed on the system throughout a training or competition session is quite high with intermittent periods of high-intensity or high training loads (Halson 2014; Colby et al. 2014). When the capacity to replenish ATP and counter the effects of inhibitory metabolites is exceeded, muscle function decreases secondary to the interaction between peripheral and central fatigue mechanisms (Faude et al. 2006; Gabbett and Domrow 2007; Noakes 2000; J. M. Davis 1995; Knicker et al. 2011; D. Caine, Caine, and Maffulli 2006).

Multiple physiological mechanisms contribute to exercise-induced fatigue (Knicker et al. 2011; Cairns et al. 2005; J. M. Davis 1995). Central and peripheral factors interact during exercise, contributing to a global physiological state that results in a decreased ability in the system to meet the physical demands of sustained sport performance (Jürimäe et al. 2011; Anish 2005; Finsterer 2012). Maintenance of athletic performance is ultimately dependent on muscle performance to produce the necessary force required to carry out a specific athletic task at the level required for optimum execution to be successful in sport (Gibson and Edwards 1985; Knicker et al. 2011). While muscle force production and integrated neuromuscular control of human movement is dependent on multiple factors, a single specific physiological mechanism that underlies the athlete's inability to sustain adequate muscle force output and coordinate complex movement during sport is elusive (Knicker et al. 2011; Cairns and Lindinger 2008; Cairns et al. 2005).

The central nervous system is responsible for signaling voluntary muscle contraction for the control of movement and maintenance of dynamic stability during sport participation (Anish 2005; J. M. Davis 1995). However, factors peripheral to the central nervous system may regulate the maximal mechanical contractile capacity of skeletal muscle, limited by energy substrate availability and skeletal muscle structural integrity (Knicker et al. 2011; Finsterer 2012; Fischer 2006). Yet, centrally originating decreases in central nervous system stimulation of skeletal muscle tissue results in decreased muscle performance. Thus, central and peripheral factors must be considered when explaining fatigue-related decreases in neuromuscular performance during high-level sport (Knicker et al. 2011; Cairns et al. 2005).

Central and peripheral fatigue factors are not independent (Anish 2005; Knicker et al. 2011). Various metabolic processes occurring systemically provide multiple forms of feedback to the central nervous system via circulating metabolites that cross the blood brain barrier, afferent feedback from sensory stimuli locally at contracting muscle, and systematically via a diverse array of autonomic nervous system receptors throughout the body (Knicker et al. 2011; Cairns et al. 2005; J. M. Davis 1995). The peripheral control of homeostasis during exercise is primarily managed by the autonomic nervous system divisions, the sympathetic and parasympathetic subsystems (Knicker et al. 2011; Cairns et al. 2005). However, the central nervous system is ultimately capable of directly modifying efferent signaling to skeletal muscle tissue via upper motor neuron synapses on alpha-motor neurons within the ventral horn of the spinal cord (Knicker et al. 2011; Anish 2005). In order to comprehensively evaluate the influence of exercise-induced fatigue on neuromuscular performance and MSK injury during sport participation, research methodology must consider parallel assessment of measures of peripheral and central factors associated with the interactive fatigue process.

The Influence of Exercise-Induced Fatigue on Neuromuscular Function and Control of Human Movement

As previously described, there are multiple biomechanical profiles that may contribute to greater ACL loading and risk of injury during sport participation. As a result of exercise-induced fatigue, three primary factors present with the potential to influence anterior cruciate ligament (ACL) injury risk; reduction in muscular performance, modification in afferent feedback to the central nervous system, and depressed cognitive function. This section will review the current evidence investigating the effects of fatigue on biomechanical variables associated with ACL loading and injury risk. This review suggests there is an interactive ecological relationship between the muscle within the peripheral physiological environment and the central nervous system. Furthermore, ACL injury literature concludes that lower extremity neuromuscular control and biomechanics significantly differ between a non-fatigued and fatigued state and mirror biomechanics associated with sport-related noncontact ACL injury (S. G. McLean and Samorezov 2009; Borotikar et al. 2008; Webster et al. 2012; Hughes and Watkins 2006; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a; Chappell et al. 2005; Cortes et al. 2012; Quammen et al. 2012).

The reduction of muscle performance as a function of force output and contraction velocity has the potential to explain some of the reported differences in neuromuscular control and biomechanics between fatigued and non-fatigued conditions. Furthermore, the potential for altered afferent feedback to the central nervous system from the periphery as well as a compromised status of the central nervous system may further support an influence of exercise-induced fatigue on injury risk, as neuromuscular control becomes depressed (Knicker et al. 2011). Additionally, there is evidence of structural compromise and subsequent decreased

function of the muscle tissue itself (Knicker et al. 2011; Brancaccio, Maffulli, and Limongelli 2007; Kraemer et al. 2013). Thus, regardless of the presence of an intact central nervous system, the intended effective action from the muscle may not be elicited with a physiological neural drive.

There is a Direct Influence of Exercise-Induced Fatigue on Neuromuscular Control and Biomechanics Associated with Sport-Related Noncontact ACL Injury

A fatigued condition during functional fatigue protocols increases the potential for a reduction in hamstring muscle activation and subsequent muscle performance (Thomas, McLean, and Palmieri-Smith 2010; Padua et al. 2006), resulting in a reduced capacity of the hamstring muscle group to oppose anterior tibial shear force at the knee joint when it is flexed less than 30°, a position at which the quadriceps musculature induces a shearing force at the knee (Kulas, Hortobágyi, and DeVita 2012; Kulas, Hortobágyi, and DeVita 2010; Thomas, McLean, and Palmieri-Smith 2010; Withrow et al. 2008; Herzog and Read 1993). Furthermore, fatigue has been observed to increase quadriceps:hamstring co-activation ratios with concomitant decreases in knee flexion (Thomas, McLean, and Palmieri-Smith 2010; Padua et al. 2006). The combined potential for a reduction in hamstring muscular force production, elevated quadriceps activation, and a decreased knee flexion angle during energy absorption in sport participation are of significant concern in fatigued athletes. Hamstring force applied at deeper knee flexion angles is described to be the primary active dynamic restraint against anterior tibial shear force, the principal ACL loading mechanism (Shimokochi and Shultz 2008; Herzog and Read 1993). Furthermore, the current body of evidence suggests exercise-induced fatigue amplifies sagittal plane lumbopelvic hip complex biomechanics linked to sport-related noncontact ACL injury; including decreased peak hip flexion angles during loading and at initial contact during various

athletic tasks (Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a; S. G. McLean and Samorezov 2009; Borotikar et al. 2008; Hughes and Watkins 2006; Chappell et al. 2005; Liederbach et al. 2014). Strikingly, fatigue exposure has been identified to increase both vertical ground reaction force and anterior tibial shear force during the early loading phase of athletic tasks, a period in which ACL loading is reported to be greatest, and when ligament failure is described to occur during injury events (Krosshaug, Nakamae, et al. 2007; Shimokochi and Shultz 2008; Yu and Garrett 2007; Chappell et al. 2005; SCHMITZ et al. 2014; Santamaria and Webster 2010). Collectively, the effects of exercise-induced fatigue on sagittal plane neuromuscular control and resultant biomechanics are worrisome in the context of sport-related noncontact ACL injury. Fatigue induces sagittal plane knee and hip biomechanics associated with ACL loading, motion observed during injury events, and elevated risk for injury.

The influence of fatigue on frontal plane biomechanics associated with sport-related noncontact ACL injury demonstrate some variability between males and females and different sport populations (Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a; Santamaria and Webster 2010). Chappell et al. observed an increase in internal knee varus moment in males and an increase in knee valgus moment in females during a stop-jump task, implicating fatigue elevates frontal plane knee loading (Chappell et al. 2005). In contrast to Chappell et al's. sex specific findings in the frontal plane, Benjaminse et al. 2008 observed a decrease in knee valgus angle during the stance phase of a landing task regardless of sex, which would agree with the kinetics observed by Chappell et al. 2005 for males, but contradict the results for females during the fatigued condition (Benjaminse et al. 2008). One potential explanation for the disparity in frontal plane knee biomechanics between Benjaminse et al's. and Chappell et al's. findings is that a running protocol for fatigue was used in Benjaminse et al's.

methods, while a squatting task was implemented in Chappell's. Additionally, Chappell et al. assessed biomechanics during a stop-jump, while Benjaminse et al. evaluated biomechanics during a drop-landing activity.

In addition to the effects of fatigue on frontal plane biomechanics at the knee, fatigue also influences lumbopelvic hip complex biomechanics during athletic tasks. In 2009 McLean et al. observed fatigue to induce greater initial contact and peak hip adduction angles during the stance phase of a cutting task (S. G. McLean and Samorezov 2009). Furthermore, McLean et al. observed an amplification in hip adduction motion with the introduction of an unanticipated cutting condition, implicating the potential for an interaction between psychological / information processing factors and frontal plane lumbopelvic hip complex neuromuscular control factors (S. G. McLean and Samorezov 2009). In agreement with McLean et al's. 2009 findings, a recent evaluation of the effects of fatigue on single-leg landing biomechanics in male and female athletes and dancers reported a increase in external hip adduction moment, which would influence a tendency toward hip adduction motion (Liederbach et al. 2014). Furthermore, male and female dancers and athletes both exhibited greater lateral trunk flexion and knee valgus moment after fatigue exposure (Liederbach et al. 2014).

McLean et al's. fatigue protocol was novel, as it was designed to induce a centrally targeted fatiguing effect with participants performing the single-leg squat fatigue task on the limb contralateral to the test-limb. McLean et al's. findings are a valuable addition to the literature, and provide insight regarding the influence of exercise-induced fatigue on central factors controlling movement. While it is difficult to establish cause and effect, McLean et al's. findings suggest that not only does exercise-induced fatigue modify human motion as a function of peripheral factors at the muscle level as previous studies have concluded, but higher level

central control of motion is susceptible to fatigue, influencing aberrations in biomechanics (S. G. McLean and Samorezov 2009).

Current literature suggests frontal plane knee and lumbopelvic hip complex biomechanics are influenced by fatigue-exposure. While the particular effect of fatigue on frontal plane knee biomechanics may be sex and task specific, there appears to be an effective increase in frontal plane knee valgus biomechanics in fatigued female athletes. Interestingly, fatigue appears to increase hip adduction biomechanics, a component of the “valgus collapse” motion observed during injury. Perhaps, the most interesting effect of fatigue on frontal plane biomechanics during athletic motion is that of an increased lateral trunk lean with concomitant knee valgus and hip adduction biomechanics, suggesting fatigue exacerbates a prospective risk factors associated with noncontact ACL injury.

The summary of the current body of evidence surrounding the influence of fatigue on biomechanics highlights the link between decreased muscle performance and an exacerbation of biomechanics associated with sport-related noncontact ACL injury. As a result of decreased muscular performance, the ability to effectively attenuate and transfer energy across the kinetic chain may be restricted in a fatigue condition. The diminished capacity to attenuate, absorb, and transmit forces safely across the kinetic chain may result in excessive forces being unintentionally transferred to musculoskeletal structures that are not well-equipped for repeated high magnitude force exposure (Sheen et al. 2013; Colby et al. 2014; Franklyn-Miller et al. 2014). Deviations in force absorption, attenuation, and transfer techniques are hypothesized to contribute to biomechanical overload (Franklyn-Miller et al. 2014). Biomechanical overload promotes excessive tissue stress such as elevated joint loading (Niehoff et al. 2011; Niehoff et al. 2010; Hamann et al. 2014; Hoch et al. 2012), higher systemic energy demands and resultant

decreases in athletic performance (Di Michele and Merni 2014; McCann and Higginson 2008; Dicharry 2010; Shimokochi et al. 2013), and an acceleration toward a exercise-induced fatigue state that may increase the probability of musculoskeletal injury secondary to manifestation of aberrant biomechanics linked to noncontact ACL injury (S. G. McLean and Samorezov 2009; Borotikar et al. 2008; Webster et al. 2012; Hughes and Watkins 2006; Alentorn-Geli, Myer, Silvers, Samitier, Romero, Lázaro-Haro, and Cugat 2009a; Chappell et al. 2005; Cortes et al. 2012; Quammen et al. 2012).

Baseline Movement Profiles Provide a Potential Explanation for Variability in Fatigue Response

Research implicates that fatigue influences biomechanical variables associated with ACL loading and injury risk. Interestingly, individuals with certain movement profiles also demonstrate biomechanical profiles linked to fatigue exposure. However, research has not yet investigated how an individual's baseline movement profile may influence their biomechanical and systemic response to high-intensity physical activity similar to the demands of field or court sports. It is possible that fatigue may exacerbate existing differences in these biomechanical variables between those with different baseline movement profiles. Therefore, inherent variation in biomechanics between those with different baseline movement profiles may be amplified in a fatigued state after exposure to high-intensity physical activity.

To date, no methodology has directly evaluated the influence of an individual's pre-fatigue movement profile on biomechanical and physiological responses to high-intensity exercise. However, two companion studies evaluated the influence of sex and activity participation-type on participants' biomechanical responses to exercise-induced fatigue during single-leg drop-landings with consideration of baseline movement profile (Orishimo et al. 2014; Liederbach et al. 2014). Part I of the investigation compared baseline movement profiles during

single-leg drop landings between male and female dancers and athletes (Orishimo et al. 2014). Epidemiological evidence implicates a higher incidence of noncontact ACL injury in athletes versus dancers (Liederbach, Dilgen, and Rose 2008; Hootman, Dick, and Agel 2007). However, the college-aged athlete population exhibits a sex disparity in noncontact injury incidence (Hootman, Dick, and Agel 2007), whereas female and male dancers appear to have similar injury rates (Liederbach, Dilgen, and Rose 2008).

While the physical demands of dance and sport are not identical, jumping, landing, and rapid changes in direction are shared motor tasks between dancing and sport participation, thus require similar biomechanical demands for participation and training (Orishimo et al. 2014; Liederbach, Dilgen, and Rose 2008). Furthermore, both athletes and dancers are subject to repeated training bouts and competition or performance sessions, thus share similar exposure to training and competition / performance stimuli (Orishimo et al. 2014; Liederbach, Dilgen, and Rose 2008). While the biomechanical demands of sport and dance are similar, ACL injury incidence varies between the two activity types. Part I of the companion evaluation hypothesized that the disparity in injury incidence patterns between dancers and athletes may be explained by the evidence implicating female athletes to exhibit inherently different biomechanics compared to their male counterparts, as well as the potential for dancers and athletes to demonstrate different biomechanics between activity participation-type groups (Orishimo et al. 2014).

Part I of the investigation observed athletes to exhibit a baseline movement profile associated with noncontact ACL injury. Athletes exhibited more lateral and forward trunk flexion and experience greater external hip adduction moment exposure during single-leg landings at baseline compared to dancers (Orishimo et al. 2014). Additionally, the authors observed a sex by activity participation-type interaction, with female athletes experiencing

greater external knee valgus exposure compared to male athletes. Thus, the hypotheses of the initial study were confirmed, identifying a disparity in lumbopelvic hip complex landing biomechanics between dancers and athletes, and a sex by group interaction in frontal plane knee loading in within athletes. These results afford the evaluation of a potential interaction between baseline movement profile and exercise-induced fatigue (Orishimo et al. 2014; Liederbach et al. 2014).

Part II of the investigation exposed the dancers and team sport athletes to fatiguing exercise in which participants were required to complete sets of 50 single-leg step-ups onto a 30 cm box, followed by 15 maximal single-leg vertical jumps. At the end of each set the athletes' and dancers' maximal vertical jump heights were assessed in conjunction with their RPE (1-10). Fatigue criteria were met when participants experienced a reduction in vertical jump height by 10% of their non-fatigued maximal jump height performance. Once fatigued, participants completed a posttest of 3 single-leg landings to assess the effects of activity participation type and sex on biomechanical responses to exercise-induced fatigue exposure. Interestingly, all participants experienced similar changes in biomechanics from pre to post-fatigue (Liederbach et al. 2014). Dancers and athletes similarly experienced increases in external hip adduction and valgus moments and increases in forward and lateral flexion when fatigued (Liederbach et al. 2014). However, on average, dancers completed more than 40% more exertional bouts to fatigue with no differences in perceived exertion during the fatiguing exercise compared to team sport athletes (Liederbach et al. 2014). The results of this study suggest that while dancers were exposed to over 40% more work, they did not experience significantly different changes in biomechanics compared to athletes.

The results from Part II of the study implicate that while dancers and team sport athletes demonstrate a similar biomechanical response to fatiguing exercise, the athlete's baseline movement profile which was associated with ACL injury biomechanics may reduce the athlete's fatigue resistance in comparison to dancers. While no direct measures of fitness or physiological markers of fatigue were compared between the groups, there were no significant differences between dancers and athletes in RPE throughout the fatigue bout. The athletes complete 40% less exertional bouts to fatigue compared to the dancers, thus the duration of the fatigue protocol was less for dancers (Liederbach et al. 2014). When considering the extended duration of the fatigue protocol in dancers without a significant difference in RPE between groups, it is evident the dancers were exposed to a significantly greater training load ($\text{RPE} \times \text{Duration}$) compared to the team sport athletes (Foster et al. 2001). It thus appears dancers can be exposed to higher training loads stimuli without suffering greater compromise of single-leg landing biomechanics compared to team sport athletes.

Collectively, the results from parts I and II of the investigation provide potential support to the notion that different baseline movement profiles may influence one's fatigue resistance. Taken together the companion studies' results provide preliminary evidence baseline movement may influence training load, a measure strongly correlated with injury rates in sport (Gabbett 2004b; Gabbett and Domrow 2007; Halson 2014). While the companion studies provide insightful information regarding the influence of baseline movement profile on biomechanical responses and fatigue resistance to high-intensity exercise exposure, the direct impact of an individual's baseline movement profile on the biological mechanisms associated with an individual's response to high-intensity exercise remain unknown. Additional research is

necessary to identify the effects of baseline movement profile on biomechanical, biochemical, physical, and psychological markers of exercise-induced fatigue.

Evidence of an Interaction Between Biomechanics and Exercise-Induced Physiological Demand on the Human Body

In order to effectively evaluate the interaction between baseline movement profile and high-intensity exercise on a high-risk female athlete's fatigue response during sport participation it is necessary to assess surrogate biological markers of fatigue. While no specific surrogate markers of fatigue comprehensively explain the underlying physiological mechanisms responsible for decreases in muscle performance that lead to the exacerbation of a biomechanical profile associated with sport-related noncontact ACL injury, multiple biochemical markers of central and peripheral fatigue mechanisms have been identified (Halsen 2014; Finsterer 2012; Rietjens et al. 2005; Knicker et al. 2011). Furthermore, the influence of baseline movement profile on biomechanical loading contributing to musculoskeletal tissue stress is not thoroughly discussed in the literature. However, the current evidence base has described biological markers that are reflective of tissue stress secondary to exposure to the demands of activities of daily life and physical activity (Kraus et al. 2011; Finsterer 2012). The aim of the following literature review is to identify viable and insightful biological markers of fatigue and musculoskeletal system stress. Specifically, this review aims to provide empirical support for the assessment of biological markers that may be sensitive to the impact of a *poor* or *excellent* baseline movement profile on an individual's physiological response to high-intensity exercise exposures.

A majority of articular biomarker research has focused on identifying biochemical markers that are representative of joint cartilage metabolism, specifically seeking to identify biomarkers representative of cartilage catabolism and those of anabolism (Attur et al. 2013;

Kraus et al. 2011; Lafeber and van Spil 2013). Recently, research has placed substantial emphasis on identifying biomarkers that are prognostic of joint degeneration, specifically markers that are representative of the osteoarthritis (OA) process (Attur et al. 2013; Kraus et al. 2011; Lafeber and van Spil 2013). While OA is not a primary concern for the healthy college-aged female athlete population, prognostic biomarkers of OA are predictive of ACL injury in physically active college-aged individuals (Svoboda et al. 2013; svoboda et al. 2012). Furthermore, previous literature has identified mode of exercise (O'Kane et al. 2006), biomechanical loading parameters (Niehoff et al. 2010; Niehoff et al. 2011), and volume (Eckstein, Hudelmaier, and Putz 2006) of exercise stimulus exposure to influence levels of biomarkers of cartilage deformation, degradation, and regeneration in the physically active population. Thus, there is utility in investigating the influence of biomechanics on cartilage metabolism.

In 2004 Andriacchi et al. proposed a theoretical framework (figure 2.1) for the study of the pathomechanics of knee OA (Andriacchi et al. 2004). Andriacchi et al.'s integrative *in vivo* OA development framework identifies a *initiation phase* that implicates aberrant biomechanics leading to a shift in the load bearing joint surface areas that are normally infrequently loaded. Andriacchi et al. suggests the infrequently loaded joint surfaces cannot tolerate the elevated frequency and magnitude of loading owing to a *progression phase* of the disease, characterized by cartilage degeneration, and ultimately breakdown (Andriacchi et al. 2004). As loading increases, Andriacchi et al. suggests the rate of disease subsequently increases. Interestingly, Andriacchi et al. proposes the study of OA development using ACL injury as a pedagogical example. Implicating those who have suffered ACL injury to demonstrate changes in biomechanics that lead to inciting the initiation phase of OA, leading to the progression phase,

explaining their elevated incidence of OA compared to the population who has not suffered ACL injury (Andriacchi et al. 2004; Lohmander et al. 2004; Lohmander et al. 2007).

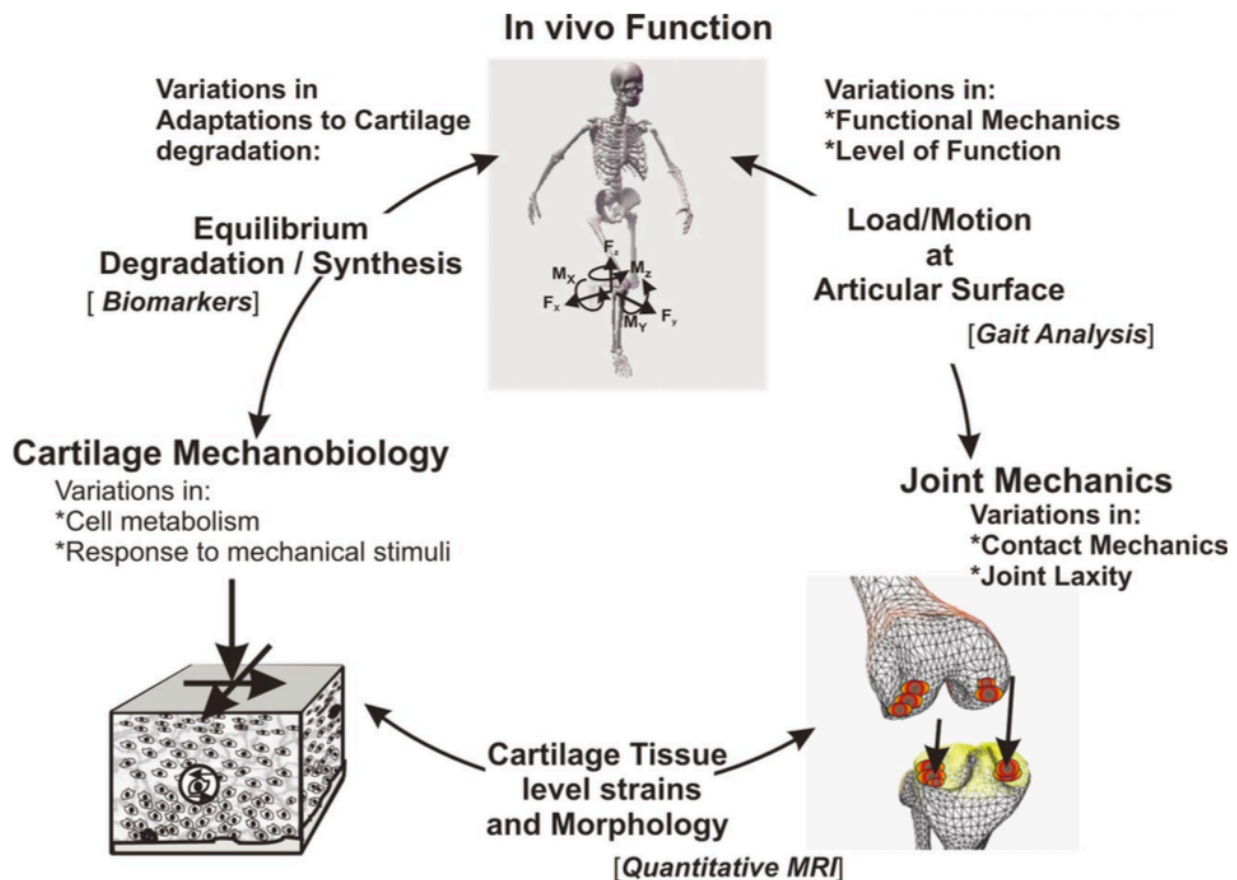


Figure 2.1. – Andriacchi et al's. 2004 theoretical framework explaining the relationship between in vivo function, non-physiological joint biomechanics, joint loading, and articular cartilage mechanical and biological responses.

It is possible that *poor* baseline biomechanics may exacerbate harmful joint loading and subsequent cartilage stress and degeneration when an athlete is exposed to high-intensity exercise. A recent large prospective case-control study (N= 90, ACL injured= 45, matched control= 45) conducted by Svoboda et al. observed elevated biomarkers of cartilage matrix destruction (Type-I & II collagen cleavage neopeptide (C1,2C) & Type-II collagen cleavage

product (C1,2C)) and cartilage matrix differentiation and production (Type-II collagen propeptides (CPII)) at baseline prior to ACL injury in a cohort of physically active military cadets (svoboda et al. 2012). Univariate analysis revealed a 1 ng/mL in serum C1,2C, C2C, and CPII concentrations were associated with a 9.1, 4.2, and 19.4 increase in odds of sustaining a ACL injury respectively (svoboda et al. 2012). Svoboda et al's. results provide evidence that variability in cartilage metabolism predicts ACL injury in the physically active college-aged population (svoboda et al. 2012). However, the specific mechanisms responsible for elevating the baseline levels of biomarkers associated with cartilage turnover (C1,2C, C2C, & CPII) in individuals at high-risk for ACL injury remain unknown. It is plausible that differences in pre-injury biomechanics between individuals with *poor* and *excellent* movement profiles may contribute to abnormal joint loading and subsequent elevations in loading of articular cartilage during activities of daily life and sport participation. Interestingly, no study has investigated the interactive effects between baseline biomechanics and exposure to high-intensity exercise on biomarkers of cartilage metabolism known to be predictive of ACL injury.

Exercise mode has been identified to influence the circulating levels of C-telopeptide of type-II collagen (CTX-II), a biomarker theorized to represent cartilage collagen breakdown (O'Kane et al. 2006; Kraus et al. 2011). Division I college endurance athletes participating in running, crew, and swimming exhibited different levels of CTx-II after athletes had been actively training for their respective sports (O'Kane et al. 2006). Swimmers exhibited the lowest levels of CTx-II when training, whereas runners had the highest levels of CTx-II. The authors concluded that while swimming and running are both metabolically demanding endurance sports with high training volumes, the biomechanical demands of swimming are inherently different than running, with running representing an exercise mode with substantially higher skeletal and articular joint

stress (O'Kane et al. 2006). Although CTx-II is representative of type-II collagen breakdown, recent reports suggest the utility of CTx-II as a viable biomarker of cartilage metabolism may be limited due to the high potential for CTx-II to represent type-II collagen breakdown from a bony tissue source versus articular cartilage (Lafeber and van Spil 2013; Lotz et al. 2013). While the CTx-II source may not be readily discernable, different biomechanical demands from various exercise modes influence type-II collagen breakdown, suggesting CTx-II is a nonspecific biomarker sensitive to variability in mechanical stress placed on the skeletal system.

Differences in mechanical loading demands have been observed to influence serum cartilage oligomeric matrix protein (sCOMP) concentrations (Niehoff et al. 2010). Within the literature sCOMP is perhaps the most commonly described biomarker of cartilage degradation, and has been accepted as a marker with substantial diagnostic, prognostic, and disease-burden/progression assessment capacities (Kraus et al. 2011; Lafeber and van Spil 2013; Lotz et al. 2013). sCOMP concentration is theorized to reflect the fragmentation of non-collagenous protein elements secondary to the extrusion of COMP fragments from loaded articular cartilage, ultimately representative of articular cartilage matrix disruption (Lotz et al. 2013; Kraus et al. 2011; Mündermann et al. 2005). The magnitude and duration of sCOMP concentration elevations are sensitive to the dose of mechanical loading (Niehoff et al. 2010; Mündermann et al. 2005).

In 2010 Niehoff et al. compared the effects of 30 min treadmill running, 30 min of slow deep knee bends (6 sets of 20 knee bends / squats to 120° over 2 min, with 3 min rest in between sets, for 120 total knee bends), and 30 min rest / lymphatic drainage laying supine on a table on circulating levels of sCOMP (Niehoff et al. 2010). Niehoff et al. observed treadmill running to elicit a significant elevation in sCOMP from baseline, whereas repeated slow deep knee bends and 30 min of supine lymphatic drainage did not result in any fluctuations in sCOMP (Niehoff et

al. 2010). The results of Niehoff et al.'s. study suggest sCOMP levels are sensitive to different modes of mechanical load exposure during exercise, implicating variability in cartilage metabolism can be explained by mechanical loading parameters. Niehoff et al. concluded that high impact, high frequency loading in running elicits an acute elevation in sCOMP reflective of cartilage degeneration, while slower controlled low impact repetitive compressive loading does not significantly stimulate cartilage metabolism (Niehoff et al. 2010).

Niehoff et al.'s. 2010 observations are supported by original research by Mündermann et al. who observed a biphasic increase in sCOMP immediately after a 30 min walking session in a healthy population (Mündermann et al. 2005). Mündermann et al. observed sCOMP to be significantly elevated immediately following 30 min of walking, then return to resting levels within 30 min, 1.5 hrs, and 3.5 hrs, and then significantly elevate again 5.5 hrs following cessation of walking exercise (Mündermann et al. 2005), whereas sCOMP levels decreased after 30-min of supine rest in a control condition (Mündermann et al. 2005). Mündermann et al. concluded the biphasic sCOMP response to loading induced by walking exercise reflects initial COMP fragmentation representative of cartilage catabolism and then a potential reflection of cartilage turnover as damaged collagen fragments are removed from the tissue and enter circulation during the anabolic repair response following cyclical load exposure (Mündermann et al. 2005). Interestingly, the observed decrease in sCOMP over the 5.5 hour period following 30-min of supine rest reflects the potential for sCOMP to be removed from circulation via lymphatic drainage, explaining the decreases in sCOMP 1.5 and 3.5 hrs post walking. Furthermore, Mündermann et al. concluded that even simple activities of daily life that may include impactful compressive loading such as walking activity prior to participation in the study protocol may

induce elevations in sCOMP, thus it is important to evaluate sCOMP after a resting baseline of at least 30 min (Mündermann et al. 2005).

While Mündermann et al. and Niehoff et al. 2010 didn't evaluate sCOMP in conjunction with neuromuscular control, biomechanics, and knee articular surface cartilage thickness measures, Kersting et al. observed a direct relationship between elevations in sCOMP and decreases in total cartilage thickness following running exercise in healthy individuals (Kersting et al. 2005). Interestingly Kersting et al. did not observe any direct influence of lower extremity kinematics or joint torques on sCOMP or femoral cartilage thickness decreases. However, Kersting et al. did observe a greater quadriceps and hamstring co-activation time during the stance phase of running gait to be associated with a greater total cartilage thickness decreases (Kersting et al. 2005). Longer quadriceps and hamstring co-activation times during the stance phase of gait are hypothesized to be associated with greater high-magnitude compressive loading of the knee joint (Kersting et al. 2005; Winter 2009). Elevated resting sCOMP, greater quadriceps and hamstring co-activation time during stance, and larger elevations in sCOMP post exercise explain total knee joint articular cartilage thickness decreases (Kersting et al. 2005). Kersting et al. did not observe an association between total knee joint cartilage thickness decreases and any kinematic or joint moment parameters. Interestingly, in agreement with Andriacchi et al.'s proposed location loading shift theory (Andriacchi et al. 2004), a site-specific positive association between tibial and patellar cartilage thickness decreases and maximum mediolateral shear forces and knee flexion-extension torques were observed respectively (Kersting et al. 2005). Collectively, Kersting et al.'s. results implicate neuromuscular control and biomechanical factors predict cartilage thickness changes in response to running exercise. Additionally, it is evident sCOMP is a viable biomarker reflective of total knee joint cartilage

thickness changes in response to neuromuscular control and biomechanical variability within the healthy population (Kersting et al. 2005).

In 2011, Niehoff et al. extended their original 2010 study to determine the effects different athletic tasks on knee cartilage response (Niehoff et al. 2011). Subsequently, Niehoff et al. compared the effects of 100 drop-landings from a 30 cm high box and 30 min of over-ground running on changes in sCOMP and knee cartilage deformation via MRI. Larger magnitude decreases in cartilage deformation were observed following the drop-landing activity compared to running, with drop-landings and running eliciting similar significant increases in sCOMP concentrations (Niehoff et al. 2011). While Niehoff et al. did not observe a significant effect for loading activity on sCOMP concentrations, a significant association was observed between sCOMP elevations and cartilage thickness decreases after the drop-landing activity only. Drop-landing activities demand a higher magnitude energy absorption, requiring greater sagittal plane motions to attenuate landing forces from flight compared to running activity (Niehoff et al. 2011). It is possible that higher impulse compressive and shearing forces are imparted on articular cartilage from drop-landings compared to running as evidence of greater cartilage deformation (Niehoff et al. 2011). Sport activity requires rapid changes in direction and landings that may impart similar (or greater) force on articular cartilage as drop-landings, thus sCOMP changes secondary to high-intensity exercise exposure comparable to the demands of sport activity may reflect articular cartilage deformation and matrix disruption.

While evidence in the healthy, athlete population does not directly link biomarkers of cartilage metabolism to lower extremity biomechanics, there is preliminary support for a positive association between external knee adduction moment impulse and CPII in the OA population (Hunt et al. 2013). Greater external knee adduction impulse is associated with greater CPII

concentrations (Hunt et al. 2013). High external knee adduction torques are consistently reported to be linked to OA progression and knee cartilage abnormalities in the pathological population (Andriacchi et al. 2004; Farrokhi et al. 2013; Kumar et al. 2014). Furthermore, pilot data implicates a lower extremity corrective exercise / strengthening program can reduce sCOMP values compared to baseline in the OA population (Hunt et al. 2013). Thus, there is preliminary evidence biomarkers of joint metabolism are sensitive to differences in biomechanics and neuromuscular control (Hunt et al. 2013).

Although it is not a direct measure of in-vivo joint biomechanics, greater body fat mass is associated with greater joint compressive force (Farrokhi et al. 2013; Runhaar et al. 2011), and has been linked to greater sCOMP values in the OA population (Bartels et al. 2014). Decreases in sCOMP have been observed with the implementation of a weight loss program inducing significant fat mass loss over 16 weeks (Bartels et al. 2014). Thus decreasing compressive joint loading secondary to weight loss is associated with decreases in circulating sCOMP (Bartels et al. 2014). Combined, the results from biomechanical, epidemiological, and intervention studies in the OA population suggest that sCOMP and CPII represent biomarkers sensitive to variability in compressive and rotational joint loads. Future study of the effects variation in biomechanics on sCOMP and CPII in the healthy athlete population may provide insight regarding the influence of a *poor* movement profile on cartilage stress.

The results of this review suggest that cartilage metabolism biomarkers that are associated with an elevated risk of ACL injury and increased cartilage deformation are sensitive to variability in biomechanics and joint loading. Specifically, it appears sCOMP is sensitive to volume of exercise exposure and can discriminate between modes of exercise and types of mechanical load exposure (Niehoff et al. 2011; Niehoff et al. 2010; O'Kane et al. 2006).

Furthermore, both CII; a biomarker representative of cartilage repair, and C1,2C; a biomarker reflective of cartilage degradation predict ACL injury risk in the college-aged physically active population (Svoboda et al. 2012). sCOMP provides insight regarding cartilage matrix status, whereas individual evaluation of CII and C1,2C permit evaluation of type-II collagen synthesis and degradation (Lotz et al. 2013). Whereas a ratio of C1,2C to CII may reflect overall type-II collagen turnover, indicative of cartilage metabolism (Svoboda et al. 2013; Lotz et al. 2013). Combined evaluation of sCOMP, CII, and C1,2C affords insight regarding the influence of a *poor* baseline movement profile on articular cartilage status in response to high-intensity fatiguing exercise.

Elevated Levels of Circulating Biological Markers of Central and Peripheral Fatigue and Exercise-Induced Muscle Damage are Associated with High Training Loads

High-intensity exercise-induced fatigue is described as complex phenomena resulting from the interaction of peripheral and central physiological factors that result in a “*failure to maintain the required or expected force (or power) output for given (sport) activity*” during sport participation (Gibson and Edwards 1985; Knicker et al. 2011). To date, no specific objective measure has been identified to comprehensively describe an athlete’s level of fatigue or training stress experienced during sport participation (Halsen 2014). The interacting multi-component nature of exercise-induced fatigue suggests it is unlikely any one marker will effectively quantify the phenomena across a broad athlete population (Knicker et al. 2011; Cairns et al. 2005; Cairns and Lindinger 2008). Currently, the most widely accepted evaluations of fatigue reflect measures of peripheral and central physiological processes that underlie an individual’s response to exercise (Halsen 2014).

External and internal training load measures are currently leveraged by sports scientists, coaches, athletes, and medical practitioners to estimate the imposed physical or mechanical demands experienced by an athlete and the athlete's subsequent physiological response to sport activity (Halsen 2014; Nunes et al. 2014; Casamichana et al. 2013; Buchheit et al. 2013). Best practices for internal and external load monitoring in athletes remains an area open for continued research, as load monitoring alone does not fully describe the mechanisms responsible for an athlete's state of exercise-induced fatigue (Halsen 2014). However, surrogate biochemical markers reflective of underlying physiological processes that contribute to exercise-induced fatigue have been described in the literature, and demonstrate significant levels of variability explained by internal and external training loads (Halsen 2014; Coutts et al. 2007; Rietjens et al. 2005; Gomes et al. 2013; Balsalobre-Fernández, Tejero-González, and del Campo-Vecino 2014; Brancaccio, Maffulli, and Limongelli 2007).

As previously described, internal (Gabbett 2004b; Gabbett 2004a) and external training loads (Colby et al. 2014; Gabbett and Ullah 2012) exhibit strong associations with injury incidence over the course of an athletic season in field and court sport athletes, thus it is possible biochemical markers of underlying exercise-induced fatigue mechanisms are similarly associated with, or explain variation in injury incidence in sport. Furthermore, a *poor* movement profile may be associated with an acceleration of fatigue physiology during sport participation. A *poor* movement profile has been implicated to provoke a higher metabolic cost relative to an *excellent* movement profile in the athlete's effort to maintain an effective work or power output during high-performance field and court sport participation (Arellano and Kram 2014; Kram and Taylor 1990; Knicker et al. 2011; Cairns et al. 2005). Therefore, the aim of the following discussion is to summarize the consensus of exercise-induced fatigue monitoring literature's identification of

promising biomarkers of fatigue mechanisms and systemic stress exposure that may be sensitive to the impact of baseline movement profile on the field and court sport athlete's mechanical load exposure and internal physiological responses to high-intensity exercise. We will describe three circulating biomarkers representative of: (1) exercise-induced skeletal muscle damage, (2) interactive peripheral and (3) central fatigue markers representative of global training stress; via serum creatine kinase (CK), serum interleukin-6 (IL-6), and serum cortisol (sCORT).

Biomarker Assessment for Training Stress & Fatigue Monitoring in Athletes

During normal exercise, systemic physiology attempts to maintain tight control of the internal environment (Anish 2005; Dallman et al. 1994; Fragala et al. 2011). Exercise or sport activity exposure represents a unique physiological stress, as the body's neuroendocrine, immune, and nervous systems function in synergy to accommodate increased physiological demands (Fragala et al. 2011; Knicker et al. 2011; Davies and Few 1973; Anish 2005). Underpinned by Hans Selye's General Adaptation Syndrome (SELYE 1950), an athlete's repeated exposure to the elevated demands of exercise stress will induce beneficial and predictable adaptations in the neuroendocrine, immune, and central nervous systems in order to more effectively and efficiently maintain an internal homeostatic environment at minimal catabolic cost to the athlete (Jürimäe et al. 2011; Kraemer and Ratamess 2005; Fragala et al. 2011; Steinacker et al. 2004). Current biomarker assessment of fatigue and training stress in sport is founded on the body of overtraining syndrome research focused on identifying a harmful disturbance of the athlete's stress-recovery state through evaluation of markers central and peripheral fatigue processes (Kellmann 2010; Nederhof et al. 2008; Kreher and Schwartz 2012). The exercise science field has been able to translate the findings of overtraining syndrome research into the development of biomarkers that are associated with various hormonal,

inflammatory, immunological, physiological (i.e. heart rate variability), and physical performance (i.e. rate of force development) markers of an athlete's stress-recovery state in response to a sport activity exposure such as a competition or training session (Kellmann 2010; Nederhof et al. 2008; Lakier Smith 2003; Lehmann, Lormes, and Opitz-Gress 1997; Petibois et al. 2002)..

Biomarkers descriptive of exercise-induced muscle damage (McLellan, Lovell, and Gass 2011b; McLellan, Lovell, and Gass 2010; McLellan, Lovell, and Gass 2011a), interactive peripheral and central exercise induced fatigue processes (Fischer 2006; Knicker et al. 2011; Anish 2005), and systematic stress (Steinacker et al. 2004; Dallman et al. 1994; VanBruggen et al. 2011) demonstrate acute and temporal responsive sensitivity to exercise intensity, mechanical or external training load exposure, and are associated with internal training load assessments, performance fluctuations, psychological affect, and competition performance in field and court sport athletes. It is possible hypothesized a greater mechanical and systemic stress induced by a *poor* baseline movement profile may influence serum creatine kinase (CK), serum interleukin-6 (IL-6), serum cortisol (sCORT) responses to high-intensity exposure in college-aged female field and court sport athletes.

Serum Creatine Kinase is Reflective of Exercise-Induced Skeletal Muscle Damage in Field Sport Athletes

Serum creatine kinase (CK) is circulating biomarker representative of structural muscle damage secondary to exposure to the biomechanical stress of muscular contraction and blunt trauma that occurs during sport participation (Brancaccio, Maffulli, and Limongelli 2007; McLellan, Lovell, and Gass 2011b). Numerous studies implicate a high-intensity training or sport competition session can substantially elevate CK levels relative to rest in elite and

recreational athletes (Brancaccio, Maffulli, and Limongelli 2007; McLellan, Lovell, and Gass 2011a; McLellan, Lovell, and Gass 2010; Silva et al. 2013; Thorpe and Sunderland 2012).

Furthermore, research suggests that serum CK levels elevate in proportion with exercise intensity and duration, suggesting serum CK is a viable marker reflective of training load (Brancaccio, Maffulli, and Limongelli 2007; McLellan, Lovell, and Gass 2011b; Johnston et al. 2013).

Serum CK levels are reflective of the release of CK into circulation from skeletal muscle that is (or was) active during athletic activity participation (Brancaccio, Maffulli, and Limongelli 2007). Representative of structural damage to muscle, CK is released from muscle tissue as a result of repeated high-magnitude eccentric contractions that occur during the stretch-shortening cycle involved in various athletic tasks (Horita et al. 1999; Nicol, Avela, and Komi 2006). In a metabolically active muscle, CK acts as a buffer to maintain the ATP-to-ADP ratio within active muscle fibers (Brancaccio, Maffulli, and Limongelli 2007). CK is an enzyme that catalyzes the reversible high-energy phosphate bonds between ADP and phosphate to form ATP from a ADP molecule and free phosphate molecule, or cleavage of a phosphate from ATP to form ADP and a free phosphate resulting in the release of energy necessary for muscular contraction (Brancaccio, Maffulli, and Limongelli 2007). Thus CK functions to help maintain the energy reservoir within muscle tissue.

Representative of structural damage to skeletal muscle, CK levels are reflective of sarcolemmic disruption (Brancaccio, Maffulli, and Limongelli 2007). Histologically, a majority of CK release is believed to originate from the sarcomere M-line, as the M-line is the only site within the myofibril that connects the thick heavy-chain myosin filaments to each other, thus providing the sarcomere with stability during muscular contraction (Brancaccio, Maffulli, and Limongelli 2007). Furthermore, histological staining suggests the M-line is the site within the

sarcomere to contain the greatest local concentration of CK (Brancaccio, Maffulli, and Limongelli 2007). During sport participation, repeated SSCs involved in athletic motions such as running, jumping, landing, and change in direction require repeated high-magnitude eccentric muscle contractions (Nicol, Avela, and Komi 2006). High-magnitude SSC eccentric contractions induce a biomechanical tensile stress across muscle tissue of sufficient magnitude to disrupt the M-line of the sarcomere, and ultimately the ultra-structure of the sarcolemma, allowing seepage of CK into circulation during sport participation and recovery (Brancaccio, Maffulli, and Limongelli 2007). Furthermore, blunt trauma to muscle tissue such as a contusion sustained during a rugby competition is capable of resulting in mechanical stress that disrupts the sarcolemma resulting in CK leakage from a skeletal muscle (Brancaccio, Maffulli, and Limongelli 2007; McLellan, Lovell, and Gass 2011b). Evidence implicates the number of athlete impacts / collisions during sport participation are directly proportional to serum CK levels (McLellan, Lovell, and Gass 2011b). CK is a biomarker that responds to the biomechanical demands of sport.

In addition to muscle damage, some evidence suggests that CK assessment may also have utility in identification of metabolically exhausted muscle tissue following exercise (Brancaccio, Maffulli, and Limongelli 2007; Finsterer 2012). A metabolically exhausted muscle exhibits a decrease in membrane resistance / stability due to elevated potassium channel openings, thus permitting leakage of CK from the sarcoplasm into circulation (Fink and Lüttgau 1976; Fink et al. 1983). Therefore serum CK may also demonstrate some value in assessment of peripheral fatigue. However, serum CK assessment alone cannot discriminate between the contribution of leakage into circulation due to potassium channel opening versus sarcolemmic disruption (Brancaccio, Maffulli, and Limongelli 2007). Furthermore, potassium channel opening alone

unlikely contributes to a high-magnitude elevation in serum CK. Therefore, it is likely elevated CK levels following exercise are primarily representative of structural muscle damage, and is a standard biomarker representative of skeletal muscle damage secondary to high-intensity exercise exposure (Brancaccio, Maffulli, and Limongelli 2007).

It is important to recognize that all muscle tissue contains CK, implicating circulating CK may originate from smooth and cardiac sources in addition to skeletal muscle (Brancaccio, Maffulli, and Limongelli 2007). While CK is present in smooth and cardiac muscle tissue, multiple reports verify that elevations in CK post exercise are driven by skeletal muscle sources (Brancaccio, Maffulli, and Limongelli 2007). Furthermore CK exists in 5 known isoforms, with 3 isoenzymes originating in the cytoplasm; CK-MM, CK-MB, and CK-BB), and 2 isoenzymes originating in the mitochondria; sarcomeric and non-sarcomeric (Brancaccio, Maffulli, and Limongelli 2007). CK-MM is primarily dominant in the skeletal muscle tissue. Cardiac muscle represents the primary source of CK-MB, being released during cardiac infarction. CK-BB is responsible for catalyzing the high-energy phosphate bond between ADP and free phosphate in brain tissue. While serum CK can originate from multiple sources, current analysis principles permit isolation of the CK-MM isoenzyme (Brancaccio, Maffulli, and Limongelli 2007).

There is ample evidence reporting serum CK levels to elevate in response to the demands of field and court sport exposure in well-trained athletes (Silva et al. 2013; Thorpe and Sunderland 2012; McLellan, Lovell, and Gass 2011b; McLellan, Lovell, and Gass 2010; McLellan, Lovell, and Gass 2011a). Serum CK elevations are proportional to external mechanical training loads (Brancaccio, Maffulli, and Limongelli 2007; Thorpe and Sunderland 2012). Interestingly, plasma CK has been observed to demonstrate a positive relationship with

the volume of sprinting activity in field and court sport athletes (Thorpe and Sunderland 2012). Specifically, percent increases in CK over pre competition levels exhibit strong associations with number of sprints ($r=0.82$), cumulative sprint distance ($r=0.92$), and cumulative high-speed running distance ($r=0.93$) during match play in elite soccer athletes (Thorpe and Sunderland 2012). Furthermore, participation in contact sport constitutes a high external load exposure to an athlete, with tackling and scrum activities adding substantial mechanical loads over noncontact or minimal contact sports (Gabbett 2012; Thorpe and Sunderland 2012). Moderate correlations between CK levels and the number ($0.62 - 0.63$) and magnitude ($r=0.61 - 0.63$) of collisions have been observed in rugby athletes 30 min – 72 hrs post-match (McLellan, Lovell, and Gass 2011b). Additionally, CK elevations are associated with lower perceived recovery status and greater muscle soreness up to 48 hrs following high-volume muscle damaging exercise (Sikorski et al. 2013) and field and court sport play (Fatouros et al. 2010). Furthermore, some evidence implicates that there is a direct association between circulating CK levels and post-match performance decrements such as vertical jump height (Johnston et al. 2013) and peak rate of force development (McLellan, Lovell, and Gass 2011a) in field and court sport athletes immediately following and up to 48 hours following competition. Collectively, the sum of CK research implicates serum CK demonstrates the capacity to explain variation in external load exposure and some measures of internal training load in response to sport activity.

Serum CK levels exhibit high variability within the population (Brancaccio, Maffulli, and Limongelli 2007). However, there is general agreement that athletes have higher resting serum CK levels compared to the non-athlete population (Brancaccio, Maffulli, and Limongelli 2007; Mougios 2007). Overall, resting serum CK levels of male ($82 - 1083$ U/L) and female ($47 - 513$ U/L) athletes have upper reference limits two-times greater than moderately active non-athletes

of similar age (Mougios 2007). In general, athletes experience a lesser magnitude increase in serum CK levels compared to untrained individuals, suggestive of training adaptation and enhanced enzymatic clearance during the recovery period following exercise exposure (Brancaccio, Maffulli, and Limongelli 2007).

While athletes may experience a lesser magnitude increase in serum CK in response to exercise, the temporal recovery kinetics for CK are similar across the population (Brancaccio, Maffulli, and Limongelli 2007), with a moderate increase in serum CK immediately following exercise and a peak elevation 24 – 48 hours following exercise termination (Brancaccio, Maffulli, and Limongelli 2007; McLellan, Lovell, and Gass 2011a). Interestingly, there is a bimodal serum CK response following exercise exposure, with an initial significant increase in serum CK occurring 0 min to 2 hrs post exercise, then a secondary peak substantially greater ($> 2\times$) than the initial post-exercise increase occurring 24 – 48 hrs post exercise (Newham, Jones, and Clarkson 1987; Horita et al. 1999; Brancaccio, Maffulli, and Limongelli 2007). The bimodal behavior of CK during recovery may be explained by secondary muscle tissue injury due to phagocytic activity after the initial inflammatory response at the initial muscle damage site (Faulkner, Brooks, and Opiteck 1993; Newham, Jones, and Clarkson 1987; Horita et al. 1999). While serum CK levels don't peak until 24 – 48 hrs following exercise termination, there is a direct association between the magnitude of the initial CK response and the latter secondary peak (Faulkner, Brooks, and Opiteck 1993; Newham, Jones, and Clarkson 1987; Horita et al. 1999; Brancaccio, Maffulli, and Limongelli 2007). Thus individuals with high initial serum CK levels immediately following exercise will demonstrate high secondary peaks 24 – 48 hrs post exercise.

While there is general agreement that there is an effect of age, sex, body mass, exercise mode, physical fitness level, and exercise environment (temperature) on resting and post exercise

CK values, CK responses to exercise in well-trained athletes demonstrate substantial variability (Brancaccio, Maffulli, and Limongelli 2007; Kraemer et al. 2013; Kraemer et al. 2009).

Specifically, athletes with chronically low resting serum CK represent a population of “low responders,” while athletes with higher resting CK exhibit a larger magnitude post-exercise elevation in serum CK as “high responders” (Godwin, Takahara, and Agnew 2010; Brancaccio, Maffulli, and Limongelli 2007). Interestingly, females demonstrate a blunted elevation in CK post exercise compared to males, with males demonstrating a relatively greater magnitude increase relative to baseline after exercise exposure. The male athletes’ greater CK elevations post exercise are partially explained by relatively larger body masses being associated with higher resting CK levels compared to female athletes’ (Brancaccio, Maffulli, and Limongelli 2007). Additionally, the blunted CK response in females is possibly explained by female secretion of oestrogen in response to exercise exposure (Tiidus 2000; Amelink et al. 1990).

Oestrogen has been observed to sustain membrane stability post exercise, restricting CK seepage from damaged muscle tissue into circulation during recovery (Tiidus 2000; Amelink et al. 1990). Although there is a relatively consistent effect of sex on resting and post exercise CK values, the male and female athlete populations demonstrate substantial intra-sex variance in CK response to exercise with “high” and “low” responders. Some variability within the male and female athlete populations may be explained by other demographics described above. However, when controlling for other demographic factors, variation lingers within discrete athlete populations (Hartmann and Mester 2000), thus it is evident there are other underlying factors that may contribute to characteristic disparities between athletes with chronically low versus those with high resting CK. It is possible a well-trained athlete’s inherent movement profile may influence

their resting CK level and their subsequent proportional elevation in CK following high-intensity fatiguing exercise.

Serum CK presents as a practical biomarker representative of exercise-induced skeletal muscle damage in the athlete. The inherent variability in the magnitude of serum CK responses to exercise between individuals appears to be dependent on resting serum CK levels (Brancaccio, Maffulli, and Limongelli 2007). While resting serum CK levels may isolate “high responders” and “low responders,” the underlying mechanisms responsible for the variance between responders remains unknown when controlling for demographics (Brancaccio, Maffulli, and Limongelli 2007; Mougios 2007; Kraemer et al. 2013; Kraemer et al. 2009). Female athletes with *poor* movement profiles may recruit a greater muscle mass to carry out athletic tasks at the same level of performance when compared to individuals with *excellent* movement profiles. A greater volume of muscle mass utilized in high-intensity exercise may contribute to higher levels of serum CK both at baseline and post exercise. Furthermore, the metabolic inefficiency of a *poor* movement profile may accelerate skeletal muscle tissue exhaustion and damage, inducing a greater relative elevation in serum CK when exposed to high-intensity sport activity compared to an *excellent* movement profile. Comparison of baseline and post exercise serum CK levels between *poor* and *excellent* movement profiles in female athletes may provide insight regarding the influence of biomechanics on skeletal muscle function during high-intensity sport activity.

Interleukin-6 as a Myokine is a Circulating Biomarker Representative of Interacting Peripheral and Central Fatigue Mechanisms

The aim of the following discussion is to describe the practicality of monitoring a peripherally produced *myokine*, interleukin-6 (IL-6), and its inhibitory influence on the central nervous system, inducing signs and symptoms of fatigue in athletes during high-intensity sport

activity. IL-6 release from skeletal muscle serves as a biochemical link between the system's peripheral physiological environment and the central nervous system during high-intensity exercise (Anish 2005; Finsterer 2012). Thus, the IL-6 myokine is a promising biomarker that can be leveraged to estimate the status of the interaction between central and peripheral mechanisms underlying exercise-induced fatigue in athletes (Anish 2005; Fischer 2006; Knicker et al. 2011).

Serum CK is not a marker reflective of the complex interplay between the periphery and the central nervous system responsible for exercise-induced fatigue observed during sport (Finsterer 2012). Parallel evaluation of biomarkers representative of skeletal muscle damage and fatigue provides a robust avenue to identify both local and central factors driving changes in athletic performance secondary to decreases in neuromuscular function (Knicker et al. 2011; Cairns and Lindinger 2008; Finsterer 2012; Anish 2005). IL-6 is widely accepted as cytokine that is responsible for the body's regulation of the inflammatory response (Brandt and Pedersen 2010). IL-6 acts both as a pro-inflammatory and anti-inflammatory cytokine identified to stimulate an immune response to tissue stress or damage (Finsterer 2012; Fischer 2006). IL-6 can be produced from virtually any somatic cell (Finsterer 2012). However, during exercise, skeletal muscle fibers are known to release IL-6 as a *myokine* (cytokine produced by a muscle fiber's sarcoplasm) (Pedersen and Febbraio 2008; Knicker et al. 2011; Fischer 2006; Finsterer 2012). The primary function of the release of IL-6 from skeletal muscle tissue during exercise is to increase energy substrate availability in effort to sustain muscle performance (Pedersen and Febbraio 2008). Recently, Brandt & Pedersen outlined the "myokine concept," describing skeletal muscle tissue to behave as an endocrine organ in response to exercise, as the release of IL-6 into circulation during and after exercise activity influences the function of distal

organ tissues to maintain systemic homeostasis (Brandt and Pedersen 2010; Pedersen and Febbraio 2008).

Locally, the IL-6 myokine stimulates muscle fiber uptake of glucose and activates fat-oxidation (beta-oxidation) pathways (Pedersen and Febbraio 2008; Febbraio et al. 2003). Peripherally, circulating IL-6 acts in a hormone-like manner, increasing hepatic gluconeogenesis and mobilization of free fatty acids into circulation from adipose tissue via lipolysis stimulation (Jürimäe et al. 2011; Pedersen and Febbraio 2008; brooks, fahey, and baldwin 2004). Collectively, the secretion of IL-6 as a myokine appears to influence both local and peripheral physiology in effort to maintain energy substrate availability for contracting muscle tissue, preserving muscle performance during field and court sport participation (Pedersen and Febbraio 2008; brooks, fahey, and baldwin 2004; J. M. Davis 1995). IL-6 release substantially increases the availability of energy substrate to contracting muscle tissue. However, the elevated physiological demands of prolonged high-intensity sport activity exposure eventually outpace the capacity of fat-oxidation, gluconeogenesis, and residual downstream carbohydrate bioenergetics to yield a sufficient energy (ATP) reservoir to maintain muscle force production (Knicker et al. 2011; Pedersen and Febbraio 2008; Cairns et al. 2005).

Interestingly, athletes report mental fatigue sensations prior to energy substrate depletion during field and court sport participation (Anish 2005; Knicker et al. 2011; Meeusen et al. 2007; Rietjens et al. 2005). Similarly, power output and performance decrements have been observed without evidence of skeletal muscle damage or of energy substrate exhaustion (Knicker et al. 2011; Twist and Highton 2013). Signs and symptoms of exercise-induced fatigue are consistently observed during acute exposures to the physiological demands of field and court sport without evidence of underlying energy substrate exhaustion or significant muscle

damage (Meckel, Machnai, and Eliakim 2008; Girard, Mendez-Villanueva, and Bishop 2011; Knicker et al. 2011; R. B. Davis et al. 1991; Anish 2005). Reductions in athletic performance during field and court sport competition or training sessions observed prior to evidence of energy substrate depletion or significant muscle damage suggest factors of central origin may influence decreases in muscle performance prior to catabolic exhaustion and biomechanical overstress (Girard, Mendez-Villanueva, and Bishop 2011; Anish 2005). Central limitation of muscle performance during sport participation has been described as a protective mechanism to maintain system homeostasis and safeguard tissues from excessive or irreversible damage (Finsterer 2012; Fischer 2006; Brandt and Pedersen 2010; Anish 2005). Interestingly, elevations in the IL-6 myokine have been identified to induce symptoms of central fatigue during exercise (Robson-Ansley et al. 2004). Thus, exercise-induced elevations of IL-6 may influence central factors of fatigue (Robson-Ansley et al. 2004; Robson-Ansley, Blannin, and Gleeson 2007; Robson-Ansley, Gleeson, and Ansley 2009).

Multiple hypotheses have been tested to evaluate the interplay between peripheral and central fatigue factors during exercise (Noakes 2000; Knicker et al. 2011; Cairns et al. 2005; J. M. Davis 1995). While it is likely more than one single factor accounts for the interaction between the periphery and the central nervous system in regards to fatigue experienced during exercise, IL-6 has been identified to have a direct effect on central fatigue symptoms and exercise performance in athletes (Anish 2005; Finsterer 2012). Furthermore, IL-6 is capable of crossing the blood brain barrier (Anish 2005). Thus, once released into circulation, IL-6 may have immediate interface with central nervous system tissue, such as the hypothalamus, which may influence the activity of the hypothalamic-pituitary-adrenal axis known to exhibit tight control over the body's stress response to exercise exposure and regulate post-exercise

metabolism (Wolfe 2001; Davies and Few 1973; Dallman et al. 1994). Regardless of the sight of its influence on the central nervous system, evidence suggests circulating IL-6 moderates central nervous system activity (Anish 2005).

The most compelling evidence linking circulating IL-6 to central fatigue symptoms is described by methodology that introduces exogenous recombinant IL-6 into circulation. In an early study, Späth-Schwalbe et al. observed acute effects of low doses of injected IL-6 to induce psychological symptoms of fatigue, elevation in depressive symptoms, and difficulty concentrating (Späth-Schwalbe et al. 1998). Furthermore, Späth-Schwalbe et al. observed significant effects of IL-6 on brainwave activity during sleep, suggestive of direct interference from IL-6 injection on central nervous system activity. Interestingly, an acute elevated secretory activity of the hypothalamic-pituitary-adrenal axis was observed with IL-6 injection versus placebo. IL-6 injection increased adrenocorticotrophic hormone and cortisol secretion with a concomitant decrease in thyroid stimulating hormone release. Späth-Schwalbe et al.'s findings are important, implicating IL-6 can substantially influence the body's primary control of homeostasis and can induce a stress response characteristic of elevated catabolic activity (Späth-Schwalbe et al. 1998). While Späth-Schwalbe et al.'s. results were focused on the effects of IL-6 on central nervous system and hypothalamic-pituitary-adrenal axis function during sleep in healthy men, the resulting evidence implicates IL-6 to have strong acute effects on the central nervous system and immunoendocrine function.

More recently, injection of recombinant IL-6 has been observed to impair running performance, invoke sensations of fatigue / tiredness, and induce mood disturbances in elite male runners compared to placebo (Robson-Ansley et al. 2004). Furthermore, IL-6 injection prior to running was observed to increase adrenocorticotrophic hormone, cortisol, and prolactin (Robson-

Ansley et al. 2004), suggesting IL-6 may influence an increase in exercise stress response, potentially promoting catabolism following exercise termination, limiting an athlete's recovery capacity (Kreher and Schwartz 2012; Rietjens et al. 2005; Halson 2014). While exogenous introduction of IL-6 provides experimental control to establish cause-and-effect between circulating cytokines and central nervous system function, nutritional intervention during exercise lends further insight regarding the physiological behavior of contracting skeletal muscle tissue and IL-6 release during exercise without invasive manipulation of IL-6 via exogenous introduction (Febbraio et al. 2003).

Febbraio et al. evaluated the effect of continuous (every 15 min) glucose ingestion on arterial IL-6 levels, net leg IL-6 release, glucose uptake, and free fatty acid uptake during a 120 min exercise bout of recumbent cycling conducted at $\sim 50\%$ $\text{VO}_{2\text{max}}$. Comparing the glucose ingestion condition to a control condition, Febbraio et al. observed significant decreases in net leg IL-6 release, arterial IL-6 levels, and free fatty acid uptake with a concomitant increase in glucose uptake. Febbraio et al.'s. results suggest that elevated glucose availability during exercise blunted IL-6 release from active skeletal muscle. Febbraio et al.'s. results are important, implicating energy substrate availability to influence IL-6 release from skeletal muscle. Furthermore Febbraio et al.'s. findings illustrate that a contracting muscle releases IL-6 prior to exhaustion, as continuous exercise at 50% $\text{VO}_{2\text{max}}$ represents a moderate intensity that can be sustained for a relatively extended duration (Medicine 2009; Garber et al. 2011; Brooks, Fahey, and Baldwin 2004). Interestingly, while there was a 20-fold increase in IL-6 mRNA transcription factors during both exercise conditions, Febbraio et al. did not observe an effect for glucose ingestion. The lack of effect of glucose ingestion on IL-6 mRNA expression is interesting considering numerous studies have observed IL-6 mRNA expression to be moderated

by pre-exercise muscle glycogen content (Fischer 2006). In general, IL-6 mRNA expression from contracting skeletal muscle has been observed to exhibit a negative association with pre-exercise muscle glycogen stores (Fischer 2006). Febbraio et al. may not have observed an effect of glucose ingestion on IL-6 mRNA due to the moderate intensity exercise in their methodology. Exercise stress maintained within a steady state may not induce substantial relatively rapid increases in IL-6 that can be observed with fatiguing interval training or sport exposure (Slattery et al. 2012; Robson-Ansley, Gleeson, and Ansley 2009; Jürimäe et al. 2011)

IL-6 myokine elevations in response to exercise are regulated by the combined influence of exercise mode, intensity, and duration (Jürimäe et al. 2011; Fischer 2006). Until recently it was assumed the IL-6 myokine response was associated with exercise-induced skeletal muscle damage (Fischer 2006). Currently it is accepted that IL-6 release from skeletal muscle can occur independent of exercise-induced muscle damage (Fischer 2006; Finsterer 2012). Furthermore, the IL-6 myokine is reported to be one of the first cytokines to elevate during exercise exposure (Jürimäe et al. 2011; Fischer 2006). Thus, IL-6 presents as a biomarker that is released into circulation prior to skeletal muscle damage, and may present as an early indicator of exercise-induced fatigue with prolonged exercise exposure (Jürimäe et al. 2011; Fischer 2006).

Inactive skeletal muscle tissue does not significantly contribute to circulating IL-6 levels during exercise, thus sport activity that requires a larger volume of muscle mass activation generally results in higher-magnitude increases in circulating IL-6 (Jürimäe et al. 2011; Fischer 2006). When discriminating between *poor* and *excellent* movement profiles, it is hypothesized that individuals with *poor* baseline movement profiles exhibit metabolic inefficiency due to greater mechanical work requirements during exercise compared to individuals with *excellent* movement profiles (Martin and Morgan 1992). Individuals with *poor* movement profiles that

require greater muscle mass activation or recruitment of synergistic muscles to carryout an athletic task may experience larger elevations in IL-6 relative to individuals with *excellent* baseline movement profiles (Dicharry 2010).

Interestingly, IL-6 responses are dependent on both exercise intensity and duration, with duration being the primary factor explaining variability in the magnitude of IL-6 elevations (Jürimäe et al. 2011; Fischer 2006). While the IL-6 response exhibits a positive association with both exercise intensity and duration, it must be considered that longer duration exercise exposure influences IL-6 variability to a greater extent than does exercise intensity (Jürimäe et al. 2011; Fischer 2006; Finsterer 2012). Thus the prudent investigator should consider the limitations of using IL-6 as a responsive biomarker in methodology deploying high-intensity, short-duration (<5 min) exercise interventions (Fischer 2006). In order to determine the influence of an individual's baseline movement profile on IL-6 response during exercise exposure, exercise intensity should be tightly controlled to isolate independent variables of interest.

IL-6 has been observed to induce symptoms of central fatigue and decrease exercise performance (Noakes 2000; Robson-Ansley et al. 2004). IL-6 responses peak at the termination of exercise (Fischer 2006; Anish 2005). Criteria that quatify fatigue as a specific percentage decrease in maximal vertical jump height in response to an exercise intervention (Coutts et al. 2007; Balsalobre-Fernández, Tejero-González, and del Campo-Vecino 2014) or use of objective criteria such as percentage of excess time required to complete a specific volume of mechanical work compared to an individual's "best" recovered performance (i.e. lowest 40 yard sprint time) are representative of muscular power reductions (Le Rossignol et al. 2014; Bishop, Girard, and Mendez-Villanueva 2011; Girard, Mendez-Villanueva, and Bishop

2011). Assessment of IL-6 following controlled termination of an exercise intervention defined by objective fatigue criteria (reflective of muscle power reduction) may permit evaluation of the effect of baseline movement profile on interactive central and peripheral fatigue mechanisms that contribute to decreased muscle performance during field and court sport participation.

Comparison of serum IL-6 responses between individuals with *poor* and *excellent* baseline movement profiles may explain peripheral and central factors driving reductions in muscular power output and neuromuscular control during sport that can contribute to biomechanics associated with noncontact ACL injury. Specifically, a central decrease in neural drive to skeletal muscle tissue may precede significant observable performance declines. Performance deficits may be mitigated or delayed by a fatiguing athlete through their exploitation of compensatory movement patterns and recruitment of synergistic muscle mass to maintain effective power output, instigating technique deviation and modified task biomechanics (Teyhen et al. 2014). While performance is maintained, individuals whom employ compensatory movement strategies in effort to maintain high-level athletic function may adopt hazardous movement profiles linked to high biomechanical tissue stresses and injurious musculoskeletal loading (Franklyn-Miller et al. 2014).

Serum Cortisol Levels Reflect the Athlete's Global Stress Response to Exercise Exposure

Cortisol is the predominant catabolic glucocorticoid secreted by the adrenal cortex in response to the human body's exposure to physical and emotional stress (brooks, fahey, and baldwin 2004). Seminal reports by Bloom et al. & Davies et al. observed moderate intensity exercise at ~60% $\text{VO}_{2\text{max}}$ is sufficient to stimulate an increase in cortisol production from the adrenal glands (Bloom et al. 1976; Davies and Few 1973). During the acute phases of exercise the primary function of the cortisol response is to maintain blood glucose levels, contributing to

metabolism regulation in response to the increased physiological demands of exercise. Circulating cortisol acts on skeletal muscle and adipose tissue, stimulating amino acid and fatty acid mobilization (Wolfe 2001; Galbo 2001; Stallknecht et al. 2001). Furthermore, cortisol stimulates the liver to produce enzymes necessary for gluconeogenic and glycogenic pathways. Mobilized amino acids and glycerol molecules (from free-fatty acid mobilization) enter the liver via circulation where they are converted into glucose and glycogen (brooks, fahey, and baldwin 2004). The synthesized glucose and glycogen molecules can be released back into circulation for tissue uptake as available energy substrates or stored in the liver (Wolfe 2001; Galbo 2001; Stallknecht et al. 2001).

Following exercise or field and court sport activity exposure, the cortisol response may vary depending on a multitude of factors such as exercise intensity (M. Viru et al. 2008; Hill et al. 2008; VanBruggen et al. 2011), the athlete's nutrition (Wolfe 2001), the athlete's training status (Urhausen and Kindermann 2002), and the individual's pre-exercise stress-recovery status (Kellmann 2010). Perhaps one of the most well-established trends regarding the exercise cortisol response following exercise exposure centers on the effect of exercise intensity. Higher intensity exercise appears to provoke a greater magnitude cortisol elevation post exercise termination compared to lower intensity exercise activities (VanBruggen et al. 2011; McGuigan, Egan, and Foster 2004; Hackney and Viru 1999; Kraemer and Ratamess 2005; M. Viru et al. 2008; Hill et al. 2008).

Furthermore, there is agreement higher intensity exercise induces rapid elevations in cortisol levels within the first 30 min post-exercise exposure, with peak elevations commonly occurring proximal to the termination of exercise or sport participation (Hackney and Viru 1999; VanBruggen et al. 2011; McGuigan, Egan, and Foster 2004; Gatti and De Palo 2010).

Conversely, moderate intensity exposures demonstrate lower magnitude increases in the cortisol response to exercise (Hackney and Viru 1999; M. Viru et al. 2008; Hill et al. 2008). Higher intensity exercise exposure also appears to increase the duration of serum cortisol elevations compared to moderate and lower intensity exercise stimuli (Hackney and Viru 1999; VanBruggen et al. 2011). Previously, it was assumed low intensity exercise exposure ($<60\%$ $\text{VO}_{2\text{max}}$) did not significantly effect cortisol levels (Bloom et al. 1976; Davies and Few 1973; Hartley et al. 1972). However, recent evidence from Viru & Hackney et al. revealed an acute rapid elevation in serum cortisol (sCORT) with exposure to exercise intensities $<50\%$ $\text{VO}_{2\text{max}}$ during a staged exercise test (M. Viru et al. 2008).

Regulation of cortisol secretion during exercise is tightly managed by the neuroendocrine system via the hypothalamic-pituitary-adrenal axis (Hackney 2006; Dallman et al. 1994; Steinacker et al. 2004; Galbo 1986). Viru & Hackney et al's findings demonstrate the tight control of systemic homeostasis (Dallman et al. 1994), suggesting blood glucose level regulation is a priority during exercise. The maintenance of blood glucose level during exercise is critical for the function and safety of the glucose-dependent brain (Steinacker et al. 2004), as skeletal muscle will readily exhaust available glucose with potentially fatal consequence if unregulated during prolonged high-intensity physical activity (Steinacker et al. 2004). The functioning of the hypothalamic-pituitary-adrenal axis represents integration of central and peripheral factors to maintain a homeostatic state during exercise exposure. Assessment of cortisol behavior is reflective of hypothalamic-pituitary-adrenal axis function during exercise. Thus assessment of sCORT levels lends insight regarding the global systemic response to the stress of exercise (Dallman et al. 1994; Hackney 2006; Galbo 1986; Steinacker et al. 2004).

There is consistent evidence supporting the positive relationship between the cortisol response and an individual's exercise intensity and training load exposure (Hackney and Viru 1999; Moreira et al. 2012; Hoffman et al. 2002; Acevedo et al. 2007; Dellal et al. 2010). Current training load monitoring best-practices recommend parallel assessment of internal and external load parameters to sufficiently assess training stress imposed on an athlete (Halson 2014). While cortisol response is accepted to be a global marker of training stress, sCORT levels should be reflective of both the athlete's mechanical load exposure representative of external load and the athlete's internal loading response. Conveniently, sCORT response has been reported to vary in proportion with both internal and external load parameters following field and court sport exposure (Hoffman et al. 2002; Moreira et al. 2012; McLellan, Lovell, and Gass 2011b; McLellan, Lovell, and Gass 2010). Currently, the effect of an individual's movement profile on internal and external load exposure is not thoroughly described. It is possible variability in movement parameters between individuals explains differences between athletes' internal training load responses' for activities of similar mode, intensity, and duration. Interestingly, a recent report by Dellal et al. compared the physiological impact of traditional straight-line high-intensity interval running activity versus shuttle running activity with similar undulating high-intensity straight-line running and subsequent recovery phases, but incorporated 180° directional changes between straight-line sprinting and recovery runs (Dellal et al. 2010). Dellal et al. designed both high-intensity interval running interventions to be of similar intensity and volume. Dellal et al. observed the intervention incorporating directional changes to induce a greater physiological response, eliciting a greater heart rate response, blood lactate elevation, and RPE. Dellal et al.'s. results reveal motion may impact physiological responses to exercise when controlling for volume and intensity exposure.

While Dellal et al.'s methodology modified biomechanical demands via task manipulation and did not evaluate the effects of an individual's inherent movement profile on their physiological response to exercise, the results of the study suggest biomechanics can modify physiological response to a controlled (similar) training stimulus (Dellal et al. 2010; Buchheit et al. 2011). Multiple studies have controlled training load stimulus with different biomechanical task demands and have observed the differences in biomechanical task demands to elicit substantial variability in physiological responses (Buchheit et al. 2011; Buchheit, Haydar, and Ahmaidi 2012; Hader et al. 2014). In a similar methodology to Dellal et al., most recently Hader et al. evaluated the combined effects of fatigue after a high-intensity running protocol and additional change in direction (COD) during shuttle run activity (Hader et al. 2014). Hader et al. compared the physiological and performance effects of a straight line shuttle run versus a shuttle run with 90° changes in direction in team sport athletes. Interestingly, Hader et al. did not observe performance decrements as measured via countermovement vertical jump and jump-landing jump height assessment. Although no performance decrements were detected, increases in blood lactate and modification in lower extremity muscle activation following the COD compared to the straight-line shuttle running (Hader et al. 2014). Specifically, Hader et al. observed a decrease in semitendinosus and lateral gastrocnemius muscular activation, which may be associated with a decrease in dynamic knee stability. Hader et al.'s results are highlight an interaction between biomechanical demand and fatigue exposure.

Together, the results of controlled training load studies evaluating the effect of biomechanical demand on physiological stress and neuromuscular control during athletic activity illustrate biomechanical demands impact an individual's systemic response to field and court sport activity. While no studies have directly evaluated the effect of biomechanical demand on

sCORT, variables such as $\%VO_{2\max}$ and blood lactate concentration are known to influence the sCORT response to exercise exposure (Steinacker et al. 2004; Mastorakos et al. 2005).

Interestingly there appears to be a consensus that while biomechanical demands may influence measures of physiological response to exercise as well as neuromuscular control factors, individuals demonstrate the ability to maintain high levels of athletic performance (Hader et al. 2014; Buchheit, Haydar, and Ahmaidi 2012; Buchheit 2012). The maintenance of athletic performance with the concomitant elevations in internal training load responses suggests that although performance is maintained the stress on the system is elevated. Collectively, these findings implicate biomechanical demand to have a significant impact on the stress of exercise.

Thus, there is substantial support for future research efforts to evaluate the impact of *poor* movement profile on global stress response to high-intensity fatiguing exercise. The current literature supports the hypothesis that individuals with a *poor* movement profile are exposed to different biomechanical, and thus physiological training stresses compared to individuals with *excellent* biomechanics. sCORT is a viable biomarker reflective of the global stress induced by exercise exposure (Steinacker et al. 2004; Anish 2005; Mastorakos et al. 2005). Investigation of the effects of baseline movement profile on an individual's global stress response to high-intensity exercise exposure provides insight regarding the possible variation in stress response to field and court sport exposure between individuals with *poor* and *excellent* movement profiles.

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CHAPTER 3

RATIONALE

The primary aim of this study is to investigate the influence of baseline movement profile on biomechanical and physiological responses to the high-intensity exercise demands of sport in female college-aged field and court sport athletes, a population at high risk for sustaining a sport-related noncontact ACL injury. The LESS is a valid and reliable clinical screening tool that is capable of identifying individuals with biomechanics associated with sport related noncontact ACL injury (Padua et al. 2009; Teyhen et al. 2014). Additionally, the LESS is able to identify individuals who demonstrate high magnitude joint loading during landing (Padua et al. 2009) that may influence an individual's physiological response to high-intensity physical activity (Hamann et al. 2014; Niehoff; Müller; Brüggemann; Savage; Zaucke; Eckstein; Müller-Lung; & Brüggemann 2011a; Niehoff et al. 2010). The LESS is a valid, reliable, and economical screening tool that requires minimal resources. Thus the LESS can be deployed across a range of clinical settings to identify individuals with *Poor* or *Excellent* baseline movement profiles (Padua et al. 2009).

Previous research suggests that manipulation of exercise mode, intensity, and duration modifies the physiological demands of physical activity and thus influences an individual's physiological response to exercise exposure (Steinacker et al. 2004; Knicker et al. 2011; Hackney 2006).

Surrogate biochemical responses to high-intensity sport participation represent underlying mechanisms driving exercise-induced fatigue responsible for a decline in muscular performance (Lambert et al. 2005; Knicker et al. 2011; Noakes 2000; Noakes 2012) that may prompt development of biomechanics linked to noncontact ACL injury during sport participation (Webster et al. 2012; McLean & Samorezov 2009; Borotikar et al. 2008; Liederbach et al. 2014). We aimed to expose a population of female athletes at high risk for sustaining a noncontact ACL injury to simulated physical demands of field and court sport participation. Following HTL exposure we evaluated changes in biochemical markers of fatigue processes, tissue damage, and biomechanics associated with noncontact ACL injury between individuals with *Poor* and *Excellent* baseline movement profiles.

Field and court sport participation has been identified to induce central and peripheral fatigue resulting in deterioration of effective muscular performance (Knicker et al. 2011; J. M. Davis 1995; Noakes 2011). HTL exposure has been identified to elevate biological markers of fatigue processes (Thorpe & Sunderland 2012; Finsterer 2012), cartilage metabolism (Niehoff; Müller; Brüggemann; Savage; Zaucke; Eckstein; Müller-Lung; & Brüggemann 2011a; Niehoff et al. 2010), and muscle tissue damage (Brancaccio et al. 2007). Pilot testing revealed that the HTL deployed in this study was capable of eliciting a high level systemic stress similar to that experienced by athletes participating in field and club sports.

The dependent variables selected for this study are reflective of underlying fatigue processes, tissue damage, and biomechanics associated with sport-related noncontact ACL injury. Biochemical markers of cartilage metabolism, fatigue processes, and muscle tissue damage are described to represent the body's physiological response to HTL or sport activity exposure (Robson-Ansley et al. 2009; Robson-Ansley et al. 2007; Halson 2014; Brancaccio et al.

2007). Interestingly, elevations in biomarkers of cartilage damage have been observed prior to and are predictive of ACL injury in the physically active population (svoboda et al. 2012). Variation in cartilage biomarker levels prior to injury may implicate there are cumulative effects of *Poor* movement on cartilage metabolism (svoboda et al. 2012). Evaluation of the influence of baseline movement profile on changes in circulating markers of joint metabolism and exercise-induced fatigue physiology is novel within the current body of ACL injury research. Integrated investigation of an individual's physiological and biomechanical responses to simulated demands of field or court sport activity may offer insight regarding the influence of baseline movement profile on noncontact ACL injury risk in the female field and court sport athlete.

POPULATION

Subjects

A total of 43 physically active females with a history of or current field of court sport participation at The University of North Carolina at Chapel Hill were recruited for this study. Female court and field sport athletes exhibit relatively high levels of physical fitness (Theiss et al. 2014), and regularly compete in athletic activities that require rapid changes in direction such as cutting, jumping and landing. Thus female court and field sport athletes experience high-frequency exposure to scenarios associated with sport related noncontact ACL injury events (Shimokochi & Shultz 2008; Shultz et al. 2010; Dai et al. 2012). College-aged female athletes that participate or participated in soccer, basketball, rugby, lacrosse, team handball, field hockey, tennis, or volleyball represent a population at high risk for sustaining a noncontact ACL injury during participation (Waldén et al. 2011; Mountcastle et al. 2007; Arendt et al. 1999; Peck et al. 2013). Thus college-aged females with a history of at least high-school varsity participation in in

soccer, basketball, rugby, lacrosse, team handball, field hockey, tennis, or volleyball were eligible for participation in this study. Specifically, eligible participants were 18 – 25 years of age, actively participating in weekly training session, performing at least 30 minutes of moderate to high-intensity physical activity a minimum of 3 days per week with a maximal oxygen uptake (VO_{2max}) ranging from 40 – 50 $ml \cdot kg^{-1} \cdot min^{-1}$. The 40 – 50 $ml \cdot kg^{-1} \cdot min^{-1}$ VO_{2max} range is representative of the college female field and court sport athlete's aerobic power (Enemark-Miller et al. 2009), and is reflective of a “good to superior” aerobic fitness level within the population (Medicine 2009). Additionally, eligible participants demonstrated a LESS baseline movement profile of *poor* with medial knee displacement or *excellent* without medial knee displacement as operationally defined by the LESS (APPENDIX 1).

LESS inclusion criteria included (Figure 3.1):

- “Stiff” or “average” sagittal plane joint displacement with the presence of the medial knee displacement error during 2 of the 3 jump-landing screening trials
- “Soft” or “average” sagittal plane joint displacement without the presence of the medial knee displacement error during 2 of the 3 jump-landing screening trials

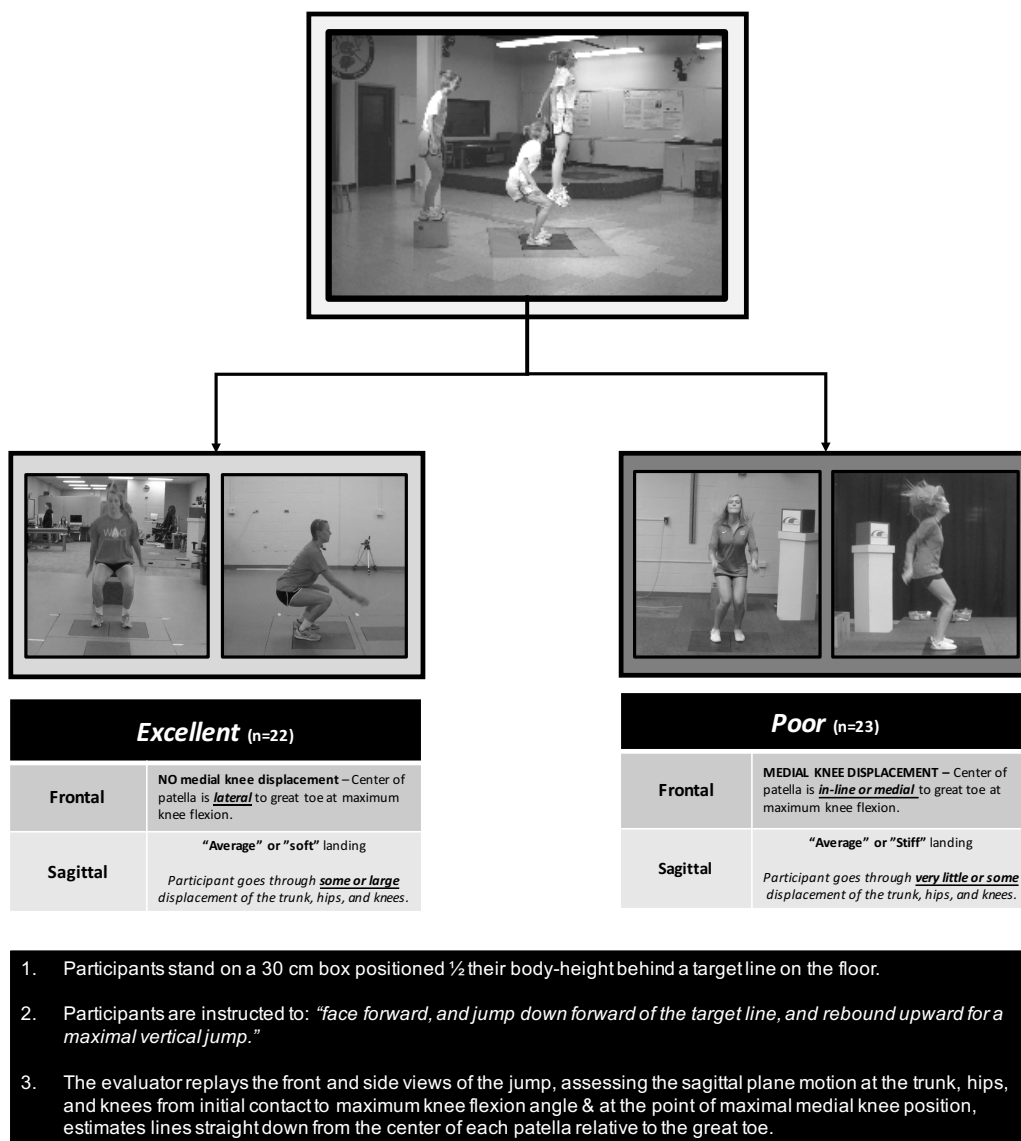


Figure 3.1 – Movement Profile LESS Inclusion Criteria.

The following exclusion criteria were applied to all participants:

- No history of lower extremity surgery within the past year
- No history of lower extremity joint surgery
- No history of prior ACL or meniscal injury
- No history of lower extremity injury in the past 6 months that prevented participation in club sport training or competition activities for more than 3 consecutive days

- No history of neuroendocrine, neurological, or metabolic disease or condition
- No history of dysmenorrhea or amenorrhea within the past 6 months
- No history of cardiorespiratory conditions that would prevent participation in high-intensity fatiguing exercise

Participants were recruited via e-mail correspondence and informational packet distribution to club team members and the student population by the principal investigator. The principal investigator also attended team meetings, training sessions or classroom lectures to recruit eligible participants.

Prior to study enrollment, eligible and willing participants meeting demographic inclusion criteria were contacted by the primary investigator via e-mail or phone correspondence for scheduling of an initial baseline movement and fitness screening. The principal investigator informed scheduled participants to report to The Sports Medicine Research Laboratory in adherence with pre-screening and testing session guidelines:

- >4 hours post-prandial
- Completely voided
- Euhydrated
- Wearing athletic apparel and running shoes
- >12 hours post most recent exercise session
- >48 hour abstinence from alcohol consumption
- >12 hour abstinence from caffeine consumption
- >7 days since administration of diuretic medication
- Received at least 6 hours of sleep the night prior

The principal investigator provided screening candidates with a document outlining pre-test guidelines (APPENDIX 2) via e-mail to promote compliance with testing standards. Candidates completed a baseline movement screening where they performed a jump-landing LESS assessment to determine if they demonstrate a *poor* movement profile with MKD or *excellent* movement profile without MKD (Figure 3.1) If participants met baseline movement profile inclusion criteria they were scheduled for a 3.5-hour data collection session (Figure 3.4) within 2 weeks of the initial screening session in The Sports Medicine Research Laboratory.

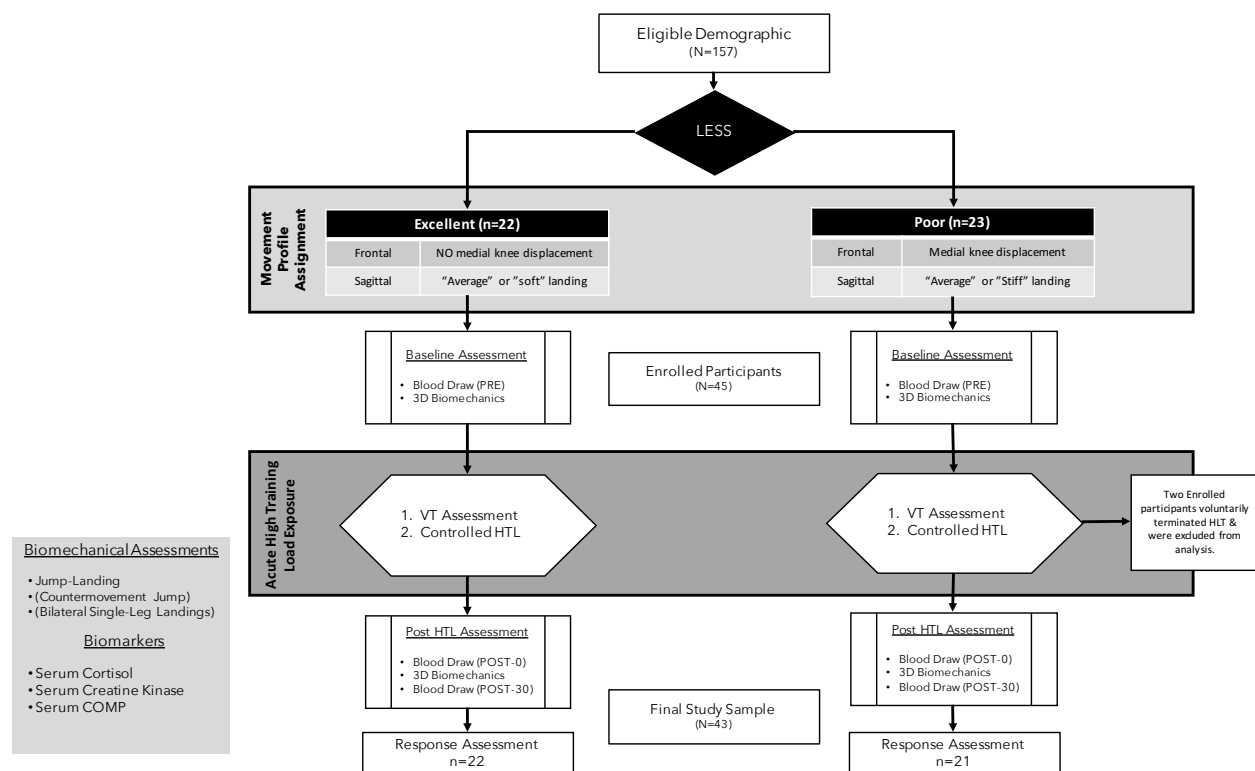


Figure 3.2 – Study Overview Diagram

Power Analysis

A *priori* power analysis of previously published data revealed that a total sample size of 30 participants (*Poor* (n=15) & *Excellent* (n=15)) allowed the investigators to detect a minimum

20% change in biomechanical and biochemical dependent variables from pre-HTL exposure to post-HTL exposure, with a power of at least 0.80 and $\alpha = 0.05$. Previous studies using repeated measures designs have observed HTL to have a moderate (Cohen's $d=0.55$) to large (Cohen's $d=2.2$) effect on sagittal and frontal plane LPHC and knee biomechanics linked to ACL injury (Chappell et al. 2005; McLean et al. 2007; Quammen et al. 2012; Liederbach et al. 2014; Cortes et al. 2012). Previous studies have reported female participants to demonstrate changes in biomechanics ranging from 21 to 96% pre to post-HTL exposure during jump-landings and side-step cutting tasks (Chappell et al. 2005; McLean et al. 2007; Quammen et al. 2012; Liederbach et al. 2014). Furthermore, HTL and sport activity exposure has been reported to induce 39 – 300% elevations in biochemical markers of cartilage metabolism (Niehoff; Müller; Brüggemann; Savage; Zaucke; Eckstein; Müller-Lung; & Brüggemann 2011a; Niehoff et al. 2010), total body stress (McLellan et al. 2010; Hackney & Viru 1999), and muscle tissue damage (Thorpe & Sunderland 2012; McLellan et al. 2010) and fatigue (Cunniffe et al. 2010).

While there is a dearth of available data comparing changes in biomechanical and biochemical dependent variables after HTL between individuals with different baseline movement profiles, recent evidence implicates differences in movement strategies between college-aged female dancers and NCAA athletes significantly influences female HTL capacity and biomechanical response to HTL (Liederbach et al. 2014). Significant differences in exercise capacity and biomechanical changes in response to HTL ranged from 33% to 40% between college-aged female dancers and NCAA athletes (Liederbach et al. 2014). Additionally, a recent pilot evaluation revealed a therapeutic exercise intervention can concomitantly decrease the presence of joint loads and circulating biomarkers linked to knee OA (Hunt et al. 2013). Thus, differences in movement profiles may significantly explain some of the reported variability in

cartilage metabolism biomarkers between individuals at high and low risk for ACL injury (svoboda et al. 2012). Thus, a study sample with 15 participants per baseline movement profile group was determined to provide adequate power to detect clinically meaningful differences in biomechanical and biochemical changes from pre to post-HTL exposure between individuals with *poor* and *excellent* baseline movement profiles.

Initial LESS Screening

Volunteers meeting demographic inclusion criteria reported to The Sports Medicine Research Laboratory for a single movement screening session. Participants were instructed to wear athletic shorts and shoes for visual observation of their lower extremity during the LESS assessment. Upon arrival to The Sports Medicine Research Laboratory, demographic inclusion criteria were verbally confirmed by the principal investigator.

LESS Instrumentation & Setup

A 8×8 meter testing area was established in the laboratory. A landing target line 0.5 meters in length was placed on the floor in the center of the testing area. Two digital video cameras (GoPro Hero 3+[®], GoPro Inc., San Mateo, California, USA) recording at 120 frames per second was positioned 1.5 m anterior (1) and to the right (1) of the landing target line arranged with their optical axes forming a perpendicular converging at the landing target line. A 30 cm box was placed at a distance exactly 50% of the participant's height posterior to the landing target line on the floor (Padua et al. 2009). The testing layout is presented in figure 3.3 below.

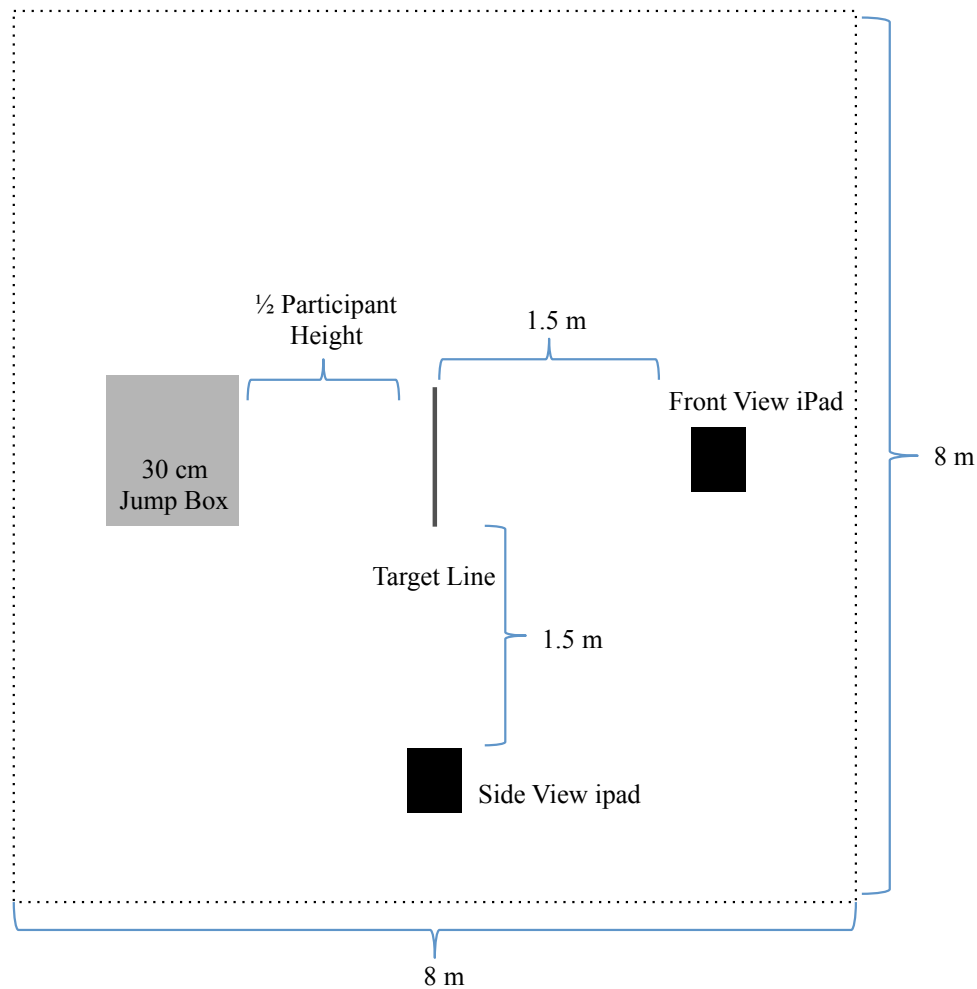


Figure 3.3 – Overhead view of the jump-landing LESS testing set-up.

LESS Screening Procedure

The participant was instructed to step up onto the 30 cm box, face forward, and “*jump down forward of the line, and rebound upward for a maximal vertical jump.*” During the jump-landing task instruction, emphasis on starting the jump in a neutral positioning with toes pointing forward, feet shoulder-width apart, and both feet leaving the box at the same time was communicated to the participant to promote a successful trial execution (Padua et al. 2009). The participant was permitted to practice the jump-landing task a maximum of three trials prior to the actual screening trials. No additional instruction was communicated to the participant during the

screening in order to minimize the influence of verbal or visual cuing / feedback on the individual's inherent baseline movement profile (Padua et al. 2009). Following the practice trials, the participant performed 3 jump-landing trials that were recorded from a front and side view. Following the jump-landing assessment the video of the front and side views were downloaded from the cameras to a MacBook Pro Computer (Apple Inc, Cupertino, CA USA). The 3 jump-landing trials were reviewed by two independent raters proficient in LESS assessment / grading reviewed the jump-landing recordings on a MacBook Pro laptop computer (Apple Inc, Cupertino, CA USA) running apple Quicktime[®](Apple Inc, Cupertino, CA USA). If the two raters disagreed on the scoring of the LESS assessment for a participant, then the principal investigator scored the assessment and a majority ruling decisions was used to determine if the participant met movement inclusion / exclusion criteria.

Participants meeting baseline movement profile inclusion criteria were scheduled for a full testing session within 2-weeks of the initial movement screening. Participants were provided with study documentation physical activity readiness questionnaire (PAR-Q), Marx activity scale, health history, menstrual cycle, and contraception usage questionnaires.

TESTING SESSION

Participants meeting all demographic and movement profile inclusion criteria returned to the research laboratory for their testing session within two weeks of their LESS assessment. Prior to leaving the screening session, the principal investigator (BF) verbally explained all pretest guidelines and provided the participants with a documentation packet outlining the study protocol and the pre-test guidelines for their personal reference. Additionally the packet contained a physical activity readiness questionnaire (PAR-Q), Marx activity scale, health

history, menstrual cycle, and contraception usage questionnaires to be completed prior to their scheduled visit. Pretest guidelines required that all participants refrain from alcohol consumption at least 48 hours prior to the testing session, refrain from using diuretic medications or supplements 7 days prior to the testing session, avoid caffeine consumption at least 12 hours prior to their testing session, maintain their “habitual” diet at least 7 days prior to testing, maintain adequate hydration at least 24 hours prior to the testing session, and achieve at least 6 hours of sleep the night before their scheduled testing appointment. The overview of the testing session is presented in figure 3.4.

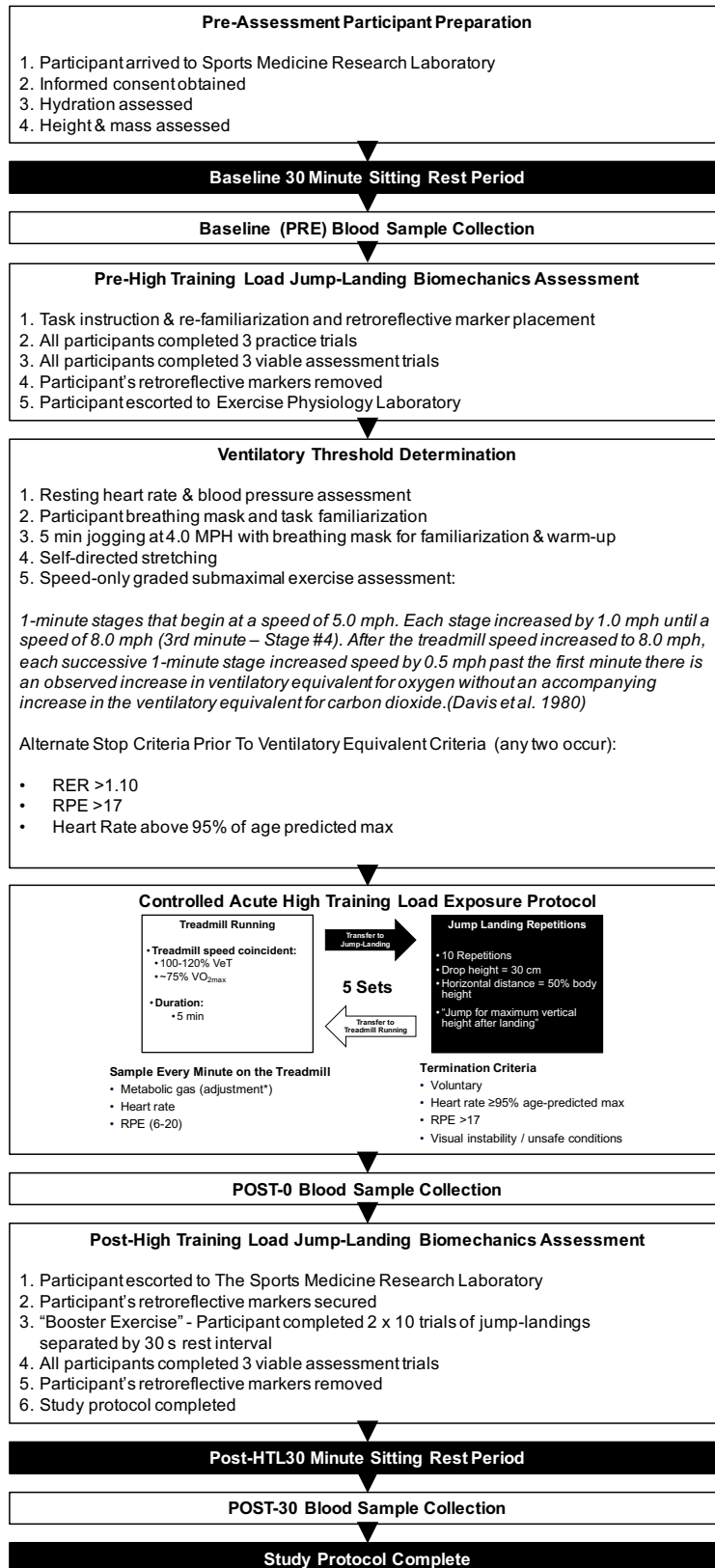


Figure 3.4 – Detailed Testing Session Overview

DATA COLLECTION

Instrumentation

Serum Sample Collection, Storage Collection, & Processing

Following the standardized 30 minute rest period, all participants had their blood drawn from their antecubital vein using a 20 G 1½ BD PrecisionGlide™ vacuutiner needle in a seated position. The blood sample was collected into a single 10 ml serum separator tube with clot activator gel (BD SST Vacutainer). The 10 ml blood sample was stored at 2 – 4°C and allowed to clot overnight prior to processing and long-term storage. Blood was collected at three separate time points during the study protocol; PRE as described above, immediately following the HTL exercise bout (POST-0), and 30 minutes after the HTL bout (POST-30). After samples clotted overnight, they were transferred to a pre-cooled centrifuge (IECCentra-8R Refrigerated Centrifuge) and were spun at 3,000 RPM for 15 minutes at 4° C. Serum was collected from the tubes via a 2.0 ml transfer a pipette into four aliquots for each time point (12 aliquots) into sterile 2.0 ml polypropylene long-term storage cryogenic vials (Nalgene Thermo Scientific). Vials were labeled, sealed, and stored at -80° C until thawing for serum biomarker analysis via ELISA procedures described below.

Biomechanical Data Collection Instrumentation

A ten-camera motion capture system (Vicon Bonita 10, Vicon Motion Systems, Los Angeles, CA, USA) interfaced with a force plate (Type 4060-10, Bertec Corporation, Columbus, OH, USA) centered within a 2×2×2 meter capture volume was used to sample three-dimensional (3D) marker trajectories (200 Hz) and ground reaction force (1,000 Hz) data using Vicon Nexus v1.7.1 motion capture software (Vicon Motion Systems, Los Angeles, CA, USA). World and

segment axis systems were established by a right hand three-dimensional Cartesian coordinate system. The positive x -axis was designated forward/anterior, the positive y -axis to the left, and the positive z -axis upward/superiorly relative to the participant (Frank; Bell; et al. 2013).

Metabolic Gas Assessment

For estimation of $\text{VO}_{2\text{max}}$ and VeT , participants completed a *speed-only* graded submaximal aerobic capacity assessment ($\text{SOVO}_{2\text{submax}}$) (Vanhoy 2012) on a motorized treadmill (GE T2100 Exercise Stress System, General Electric – Healthcare, Little Chalfont, UK) with measurement of respiratory gas exchange using a metabolic cart (TrueOne 2400 Metabolic Measurement System, Parvo Medics, Sandy, Utah, USA) and instantaneous monitoring of heart rate (A39 Exercise Monitor, Under Armour Inc., Baltimore, Maryland, USA). Prior to the submaximal aerobic capacity and ventilatory threshold assessment, the principal investigator completed standard calibration procedures of the flow, carbon dioxide, and oxygen sensors of the metabolic cart using a 3.0 L syringe of known gases. The principal investigator described the $\text{SOVO}_{2\text{submax}}$ assessment protocol to the participant before the initiation of the evaluation procedures. After the principal investigator delivered testing instructions and explained the assessment procedures, the participant's resting heart rate (Under Armour A39, Under Armour Inc., Baltimore, Maryland, USA), blood pressure (ADC 700 Diagnostix[®] Series Pocket Aneroid Sphygmomanometer, American Diagnostics Corporation, Hauppauge, New York, USA; 3M[™]Littmann[®] Stethoscope, 3M, St. Paul, Minnesota, USA), and blood lactate levels (Lactate Plus, Nova Biomedical, Waltham, Massachusetts, USA) were measured and recorded after lying supine for 5 minutes. The principal investigator reviewed the participant's resting vital signs and

ensured there were no evidence of contraindications to participation in a submaximal intensive exercise assessment or abnormalities in resting blood lactate concentrations (Medicine 2009).

Once the principal investigator determined the participant was free of contraindications for exercise testing, the participant completed a 5-minute warm-up on the treadmill at 4.0 miles per hour (mph), after which they completed a light self-directed stretching protocol. Following the warm-up, a member of the research team instructed the participant to sit atop a chair placed on the treadmill belt. Once sitting in the chair, the participant was fitted for a closed-circuit mouthpiece interfaced to the metabolic cart for measurement of ventilatory gas exchange during the $\text{SOVO}_{2\text{submax}}$ testing protocol and HTL exercise exposure. The mouthpiece was secured comfortably around the participant's head, covering the mouth and nose. The principal investigator ensured a patent seal between the ventilation mask and the participant's face by having the participant forcefully exhale and inhale a minimum of 5 ventilations to minimize escape of ventilatory gases during the $\text{VO}_{2\text{max}}$ assessment. After a patent seal and adequate ventilatory flow was confirmed, the participant continued to sit on the chair atop the treadmill belt for at least 3 minutes to allow for participant familiarization with breathing through the ventilatory gas exchange apparatus. Once the participant was comfortable breathing through the ventilation monitoring apparatus, the principal investigator once more verbally explained the graded maximal exercise protocol and ensured the participant understood the testing procedures.

The $\text{SOVO}_{2\text{submax}}$ protocol consisted of 1-minute stages that begin at a speed of 5.0 mph (Table 3.1). Each stage increased by 1.0 mph until a speed of 8.0 mph (3rd minute – Stage #4). After the treadmill speed is increased to 8.0 mph, each successive 1-minute stage increases speed by 0.5 mph until the candidate Each stage increased by 1.0 mph until a speed of 8.0 mph (3rd minute – Stage #4). After the treadmill speed increased to 8.0 mph, each successive 1-minute

stage increased speed by 0.5 mph past the first minute until there was an observed increase in ventilatory equivalent for oxygen without an accompanying increase in the ventilatory equivalent for carbon dioxide or achieved an RPE of >17 , RER 1.10, or 95% age-predicted maximal heart rate once any of the above criteria were met, the testing protocol was completed and terminated (Medicine 2009; Berry 2012; Vanhoy 2012; J. A. Davis et al. 1980). The participant's oxygen uptake, RER heart rate, RPE (6 – 20) (Borg 1970), and respiratory exchange ratio were recorded at the end of each completed stage and at the instant of voluntary termination. The participant was informed they can voluntarily terminate the testing protocol at any time throughout the protocol with a “thumbs-down” signal to the research team.

Stage (1-min intervals)	Speed (mph)
1	5.0
2	6.0
3	7.0
4	7.5
5	8.0
6	8.5
7	9.0
8	9.5
9	10.0
10	10.5
11	11.0
12	11.5
13	12.0
14	12.5

Table 3.1 Speed-Only Graded Submaximal Aerobic Power Assessment Protocol

Upon meeting $\text{SOVO}_{2\text{submax}}$ protocol stop criteria, the treadmill was slowed to a full stop. A member of the research team placed a chair atop the treadmill belt, assisting the participant to

a sitting position. The research team then removed the ventilation mouthpiece and heart rate monitor. A research team member then assisted the candidate in stepping off the treadmill to a chair in the Integrated Exercise Oncology Laboratory, where they sat resting for 3-minutes at which point a post-SOVO_{sub2max} blood lactate sample was collected, analyzed and recorded.

Following completion of the ventilatory threshold assessment via the SOVO_{2submax} protocol, the participant's ventilatory threshold was determined using a modified V-slope method (Sue et al. 1988) to identify when there was an observed increase in ventilatory equivalent for oxygen without an accompanying increase in the ventilatory equivalent for carbon dioxide (J. A. Davis et al. 1980) in the participant's respiratory gas exchange data sampled during the assessment protocol. The VO₂ and treadmill speed coincident with 100%, 110%, and 120% were identified, and used to define the control of the treadmill running speed during the HTL protocol (figure 3.4) (Albouaini et al. 2007). Regardless of achieving a true maximal test, candidates who achieved an oxygen uptake within the predicted 40 – 50 ml•kg⁻¹•min⁻¹ VO_{2max} range during the SOVO_{2submax} protocol were included in the study sample unless prediction equations implicate a VO_{2max} greater than 50 ml•kg⁻¹•min⁻¹ may have been achieved by the participant representing a “true max” test.

Participants achieving a projected 40 – 50 ml•kg⁻¹•min⁻¹ VO_{2max} and demonstrating either a *poor* or *excellent* baseline movement profile continued to participate in the study procedures described below, and underwent exposure to the HTL exercise bout and post-HTL assessments for inclusion into the study sample representing an individual meeting demographic, movement profile, and fitness level inclusion criteria.

Procedures

A diagram outlining the data collection procedures and protocol sequence is provided in figure 3.4 above.

All procedures were approved by the biomedical institutional review board (IRB) at The University of North Carolina at Chapel Hill. Enrolled participants reported to the laboratory for a single-testing session. To control for the diurnal variation of cortisol (Kirschbaum et al. 1999), all participants reported to the research laboratory between 14:00 and 16:00 for their testing sessions. Upon arrival to the research laboratory informed consent was obtained prior to initiation of the study protocol outlined in figure 3.4. After informed consent was obtained, the principal investigator verified the information in the pre-test questionnaires to confirm the participant had no contraindications for exercise and met inclusion criteria.

Upon completion of informed consent and inclusion criteria verification procedures, participants provided a mid-stream urine sample for evaluation of their hydration level using the specific gravity technique via refractometry (TS Meter, American Optical Corp., Keene, New Hampshire, USA) to ensure adequate hydration (urine specific gravity ≤ 1.02) prior to exercise (Stuempfle & Drury 2003). Height (cm) and mass (kg) were measured and recorded using stadiometer and a digital scale (Detecto 2381, Detecto, Webb City, Missouri, USA).

Prior to collection of the participant's baseline blood sample collection, they sat atop a treatment table in the research laboratory for exactly 30 minutes of rest. Participants were instructed to not step down from the table to ensure standardization of baseline blood samples in efforts to limit the effects of previous daily activity on cartilage, muscle and stress biomarkers at baseline (Niehoff; Müller; Brüggemann; Savage; Zaucke; Eckstein; Müller-Lung; & Brüggemann 2011b).

Study Protocol

Blood Sample Collection: Following the standardized 30 minute rest period, all participants had their blood drawn from their antecubital vein using a 20 G 1½ BD PrecisionGlide™ vacuutiner needle in a seated position. The blood sample was collected into a single 10 ml serum separator tube with clot activator gel (BD SST Vacutainer). The 10 ml blood sample was stored at 2 – 4°C and allowed to clot overnight prior to processing and long-term storage. Blood was collected at three separate time points during the study protocol; PRE as described above, immediately following the HTL exercise bout (POST-0), and 30 minutes after the HTL bout (POST-30). After samples clotted overnight, they were transferred to a pre-cooled centrifuge (IECCentra-8R Refrigerated Centrifuge) and were spun at 3,000 RPM for 15 minutes at 4° C. Serum was collected from the tubes via a 2.0 ml transfer a pipette into four aliquots for each time point (12 aliquots) into sterile 2.0 ml polypropylene long-term storage cryogenic vials (Nalgene Thermo Scientific). Vials were labeled, sealed, and stored at -80° C until thawing for serum biomarker analysis via ELISA procedures described below.

Baseline Biomechanical Testing Battery Preparation: Participants donned non-reflective spandex shorts and a sports bra. The principal investigator secured rigid clusters of retroreflective markers on the participant's dominant lower extremity (side subject identified they would use to kick a soccer ball for maximum distance) at the dorsal surface of the shod foot, midpoint of the anterolateral shank, midpoint of the anterolateral thigh, and sacrum using double-sided tape and athletic pre-wrap. After the rigid clusters were secured, the principal investigator attached individual retroreflective markers to the dominant limb's medial and lateral ankle malleoli, femoral condyles, bilateral anterior superior iliac spines, and bilateral acromion processes.

A static trial was collected with the participant facing the positive x -axis of the world coordinate system. Markers were removed from the medial and lateral epicondyles, ankle malleoli, and bilateral anterior superior iliac spines after the static trial. All kinematic and kinetic data were imported into The Motion Monitor v9.0 software system (Innovative Sports Training, Inc., Chicago, IL, USA) to calculate joint angles, internal joint moments, and ground reaction force vector components. Baseline biomechanics were evaluated during the jump-landing task using the calibrated 3-dimensional motion capture system. Prior to participant preparation for motion analysis, the principal investigator described the jump-landing task. The participant was permitted to complete 3 practice trials of the jump-landing task (Frank; Bell; et al. 2013).

Jump-Landing: The jump-landing trials were completed in the calibrated 2×2×2 meter laboratory capture volume. The jump-landing task protocol was synonymous with the jump-landing protocol for the LESS but incorporated 3-dimensional motion capture during the study protocol described by Padua et al. 2009. A 30 cm box was placed at a distance 50% of the participant's height from the leading edges of the right and left force platforms. The participants were instructed to step up onto the 30 cm box, face forward, and *“jump down to the center of the force plates, and rebound upward for a maximal vertical jump.”* During the jump-landing task instruction, emphasis on starting the jump in a neutral positioning with toes pointing forward, feet shoulder-width apart, and both feet leaving the box at the same time was communicated to the participant to promote a successful trial execution. Participants completed a total of 5 jump-landing trials. Any trial where the participant did not leave the box with both feet simultaneously, failed to execute the jump-landing, did not land with their feet completely on a single force platform, exhibited an excessive vertical trajectory off the box prior to landing, or jumped forward off the ground was discarded and repeated (Padua et al. 2009).

Ventilatory Threshold Assessment: A member of the research team will walk participants who meet baseline movement profile inclusion criteria to The Integrated Exercise Oncology Research Laboratory located within 100 feet of The Sports Medicine Research Laboratory for completion of a graded submaximal aerobic capacity fitness assessment (SOVO_{2submax} assessment). Upon arrival to The Integrated Exercise Oncology Research Laboratory, a member of the research team measured and recorded the participant's height and mass with a stadiometer and balance beam scale (Detecto 2381, Detecto, Webb City, Missouri, USA). The participant then completed the SOVO_{2submax} protocol as described above.

High Training Load Exposure Protocol: After briefing, participants were asked if they have any questions prior to initiation of the HTL protocol.

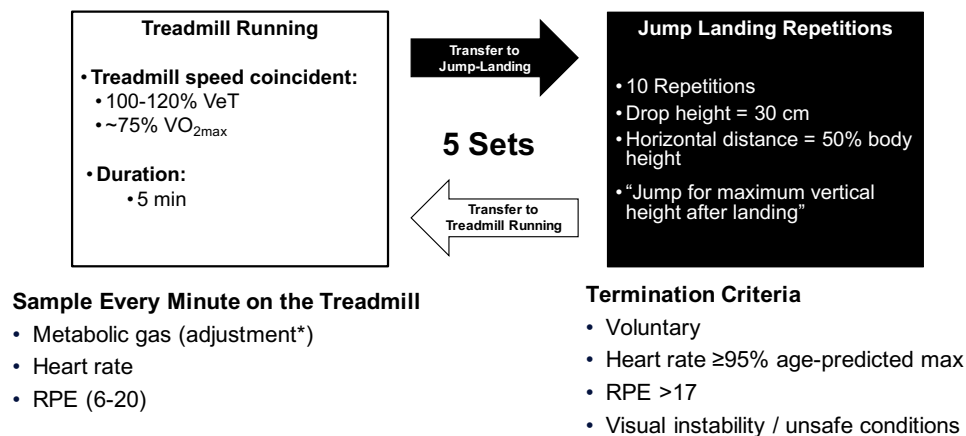


Figure 3.5 – High Training Load Exposure Exercise Protocol

A mouthpiece was fitted to the participant for monitoring of ventilatory gases during treadmill running during the HTL protocol. The individual began the HTL protocol running on a treadmill at a running speed (intensity) coincident with 115 - 120% VeT (~75% of their VO_{2max}) for 5 minutes. After the participant ran for 5 minutes, they then stepped off and straddled the

treadmill belt, a research team member removed the ventilation mouthpiece and assisted the participant as they stepped down off the treadmill to the floor. Once off the treadmill, the participant initiated the jump-landing interval of the HTL protocol, stepping atop a 30 cm box placed at a distance 50% the participant's body height posterior to a target line on the floor.

Similar to the jump-landing task during the LESS assessment, the participant was instructed to jump down forward of the target line on the floor, and then immediately jump upward for maximum height. The participant completed 10 repetitions of the jump-landing prior to stepping back onto the treadmill for initiation of the next 5-minute running interval. The combination of the 5-minute running and 10 jump-landings represents a single set of the HTL protocol. Participants completed 5 sets of the HTL protocol for a total volume of 25 minutes of running at 100 – 120% $\dot{V}_{E,T}$ and 50 jump-landings. A member of the research team recorded RPE (6-20), heart rate, $\dot{V}O_2$, and RER data during each minute of the HTL protocol set. Members of the research team verbally encouraged participants throughout the HTL protocol with consistent motivational cuing between each participant. If at any point during the HTL protocol participants noted that they could not physically continue or experienced pain, the HTL protocol was terminated with participants giving a “thumbs-down” signal.

Post-Exercise Assessments: Immediately following the final (5th) set of the HTL protocol a blood lactate and immediately post (POST-0) blood sample was collected as described above. Following post-exercise venous blood sample collection, a member of the research team quickly escorted the participant back to The Sports Medicine Research Laboratory. Upon arrival, members of the research team rapidly re-applied and secured retroreflective markers and marker clusters with double-sided tape, pre-wrap, and white athletic tape as necessary and a static trial was collected as described previously. After a static trial was collected to establish a viable 3D

biomechanical model the participants completed two sets of ten “booster exercise” jump-landings separated by 30 seconds of rest to offset recovery that may have occurred during marker attachment. Following the “booster exercise,” the participants completed three additional trials of the jump-landing task to evaluate post-HTL jump-landing 3D biomechanics. Following the last jump-landing assessment, retroreflective markers were removed and the participant laid supine on a treatment table in The Sports Medicine Research Laboratory. After 30 minutes of supine rest, a 20-minute post (POST-30) blood sample was obtained in the exercise oncology laboratory. Upon the collection of the POST-30 blood sample, the study protocol was completed and the participant was excused from the laboratory.

DATA PROCESSING & REDUCTION

Blood Sample Processing & Long-Term Serum Sample Storage Preparation

Once all biomechanical and blood sample collection processes are complete, the primary investigator transported the 10 ml baseline and post-HTL SSTs on ice to The University of North Carolina’s Applied Physiology Laboratory located within 100 feet of The Sports Medicine Research Laboratory. The samples were allowed to clot overnight at 2 – 8° C. After clot formation, samples were be centrifuged at 1000 g (3,000 RPM) for 15 minutes at 4° C. Centrifuged samples were evaluated for quality; specifically noting any hemolytic or turbid samples. Appropriate quality control measures were employed for compromised samples to determine if the sample was viable. Viable serum samples were evenly divided into four aliquots and pipetted into sterile 2.0 ml polypropylene long-term storage cryogenic vials. Vials were labeled, sealed, and stored at -80° C until thawing for serum biomarker analysis via ELISA.

Marker Identification & Processing

All kinematic and kinetic data were imported into The Motion Monitor v9.0 software system (Innovative Sports Training, Inc., Chicago, IL, USA) to calculate joint angles, internal joint moments, and ground reaction force vector components. Kinematic data were filtered using a 4th order low pass Butterworth filter at 20 Hz (Yu et al. 1999). Net internal joint moments were derived using an inverse dynamics procedure, representative of the combined influence of soft tissue forces acting about a joint (D. Gagnon & Gagnon 1992; Winter et al. 1974). Data were then exported and reduced using a customized software program to calculate the dependent variables of interest (Matlab v2016b, The Mathworks, Inc., Natick, MA, USA). Sagittal plane trunk motion was calculated as the trunk segment relative to the world axis system. Dominant limb hip joint motion was defined as motion of the thigh segment relative to the pelvis segment using a Cardan angle sequence of Y ((+) extension/(-) flexion), X' ((+) adduction/(-) abduction). Dominant limb knee joint motion was defined as the motion of the shank segment relative to the thigh segment using a Cardan angle rotation sequence of Y ((+) flexion/(-) extension) (Wu et al. 2005). Frontal plane knee motion was defined by as a combined segment angles of the thigh and the shank segments rotation relative to the world x -axis ((+) valgus (or tibial abduction)/(-) valgus (tibial adduction)) to avoid multi-planar cross talk that occurs with excessive medial knee displacement (Frank; Blackburn; et al. 2013). Medial knee motion (displacement) was calculated as the difference between the instantaneous value of the y -axis position of the center of the knee joint and the y -axis position of the knee joint center at initial contact with respect to the world axis system (Bell et al. 2013).

Kinetic Calculations

Ground reaction force and center of pressure data and interpolated segment kinematic data were used to derive net internal knee and hip joint moments using inverse dynamics procedures described by Gagnon & Gagnon et al. and Winter (D. Gagnon & Gagnon 1992; Winter 2009). Net internal sagittal plane knee moment represents the combined influence of soft tissue forces acting about the knee joint's medial-lateral axis of rotation (y -axis). Net internal sagittal plane hip joint moment represents the combined influence of soft tissue forces acting about the hip joint's medial-lateral axis of rotation (y -axis). Net internal frontal plane knee moment represents the combined influence of soft tissue forces acting about the knee joint's anterior-posterior axis of rotation (x -axis). Net internal frontal plane hip joint moment represents the combined influence of soft tissue forces acting about the hip joint's anterior-posterior axis of rotation (x -axis). Proximal ATSF was calculated as the net anteriorly directed shearing component of the force acting at the knee joint along the proximal tibia's x -axis (Chappell 2005). Vertical ground reaction force was calculated as the pure vertical component of the ground reaction force vector coincident with the world z -axis.

Data Reduction

Biomarker Data Reduction: The selected systemic stress, cartilage, and muscle tissue stress biomarkers were analyzed using commercially available ELISA kits (abcam cortisol, Abnova COMP, MyBioSource CK-MM). All biomarkers were assessed at PRE for a baseline value. The post HTL values for Cortisol and CK-MM were assessed at POST-30 (Hackney & Viru 1999; Brancaccio et al. 2007), while the post HTL values for COMP were assessed at POST-0 (Niehoff; Müller; Brüggemann; Savage; Zaucke; Eckstein; Müller-Lung; &

Brüggemann 2011b). The results of the biomarker assays were assessed in duplicate using a 96 well, 8-channel microplate reader (ChroMate[®] 4300, Awareness Technology Inc., Hauppauge, New York, USA). Cortisol was read at 450 nm, COMP at 405 nm, and CK-MM at 450 nm per manufacture guidelines. All samples from an individual participant were analyzed on a single ELISA plate. The intra-assay coefficients of variation for cortisol, COMP, and CK-MM were 1.57%, 5.88%, and 7.14% respectively. The inter-assay coefficients of variation for cortisol, COMP, and CK-MM were 4.48%, 3.20% and 11.1% respectively.

Biomechanical Data Reduction: All segment kinematic and kinetic data, and ground reaction force data were processed in the Motion Monitor software package. A Butterworth 4th-order zero-phase lag digital filter was applied to all kinematic data using a 20 Hz cutoff frequency to optimize filter sharpness and roll-off efficiency, maximizing the signal-to-noise ratio of the kinematic data (Yu et al. 1999). Filtered segment kinematic and derived internal moment data were interpolated and aligned with the raw 1,000 Hz ground reaction force data. Thus, all continuous biomechanical data were interpolated exported from the Motion Monitor software at an effective 1,000 Hz sampling frequency.

Filtered segment biomechanical data and raw ground reaction force data were exported from the Motion Monitor software package for import into a custom MatLab software program (MatLab v2016a, Mathworks, Natick, Massachusetts, USA) for further data reduction. Following data import into the custom MatLab program, the stance phase for the jump-landing task was identified from ground reaction force data. All biomechanical data were calculated during the stance phase of the jump-landing task defined as the point of initial ground contact to toe-off. Initial ground contact was defined as the first time point the vertical ground reaction force exceeded 10N. Toe-off was defined as the first time point from initial ground contact that the

vertical ground reaction force was than 10N (Padua et al. 2009). All biomechanical variables from the jump-landing were calculated during the stance phase.

DATA ANALYSIS

All results were analyzed using SPSS statistics (Version 21 IBM). Descriptive statistics for biomarker, participant anthropometric data, and metabolic data collected during the HTL were calculated. The level of significance for all hypothesis tests was set at $\alpha < 0.05$ *a priori*. Independent samples *t*-tests were carried out to determine if there was a difference in anthropometrics and fitness levels between movement profile groups. A 2×5 mixed model analysis of variance (ANOVA) was carried out to determine if there was an effect of movement profile on metabolic data across the stages of the HTL.

Biomarker Analysis

Due to the inherent variability in raw biomarker data, all raw serum concentrations were natural log transformed to establish normality for statistical analyses using a 2×2 mixed model ANOVA to evaluate the effects of group and time on biomarker concentrations pre and post HTL. *Post hoc* analyses using group-by-time means and 95% confidence intervals were used to evaluate multiple comparisons. The lack of overlap between 95% confidence intervals around group-by-time means was used for criterion for statistical significance (Poole 2001; Dijkers 2013). Additionally, independent samples *t*-tests were carried out to compare $\Delta\%$ scores for raw biomarker data to further evaluate the presence of a significant difference in a biomarkers response to HLT between groups (Fitzmaurice 2001; Fitzmaurice et al. 2011). The log

concentrations of biomarkers were backwards log transformed for data presentation and interpretation within the context of previous literature.

Although systemic and tissue stress biomarker levels were assessed for all participants, in some samples, individuals presented with levels outside a physiological range, did not have viable pairs of pre and post HTL secondary to compromised sample integrity, or presented as statistical outliers >2 standard deviations outside the log-transformed group-by-time sample means. To control for missing data, a list-wise deletion was applied such that the final number of participants with valid pre and post HTL values for cortisol was (*excellent* (n=19), *poor* (n=21)), COMP was (*excellent* (n=21), *poor* (n=20)), CK-MM (*excellent* (n=21), *poor* (n=18)). Finally, chi-square analyses of association were carried out to determine if there was an relationship between movement profile group with “responders” who increased their levels of circulating biomarkers or “non-responders” who maintained or decreased their levels of circulating biomarkers of interest.

Biomechanical Analysis

All biomechanical data were analyzed as continuous normalized waveforms during the stance phase of the jump-landing (Kuenze et al. 2014). Kinematic and kinetic data were normalized to 201 data points (knots) over the stance phases of the three jump-landing task trials using a cubic spline function. Previous studies have described the stance phase duration to range from 190 to 374 milliseconds during jump-landing tasks (Cowley et al. 2006; Strutzenberger et al. 2014). Thus, use of 201 knots derived from 1,000 Hz raw and interpolated kinetic and kinematic data points provided sufficient resolution of biomechanical variables of interest during

the jump-landing task. Each knot was calculated as the mean value of the respective derived knots from each of the three jump-landing tasks (eq. 1) (trial 1, trial 2, trial 3).

$$Knot_{i...201} = \frac{Knot_{i\ t1} + Knot_{i\ t2} + Knot_{i\ t3}}{3}$$

(eq. 1)

To calculate changes in biomechanical variables from baseline to post-exercise, the differences between the respective individual baseline and post-HTL knot values ($knot_{bi}$ & $knot_{fi}$) was calculated to form a 201 knot waveform reflecting the change in the biomechanical variable of interest (eq. 2).

$$Knot_{\Delta i...201} = Knot_{fi} - Knot_{bi}$$

(eq. 2)

Change score waveforms were calculated for all biomechanical variables of interest, representative of the participant's biomechanical response to HTL.

Pre-HTL, post-HTL, and change score frontal and sagittal plane kinematic and kinetic variable ensemble means and associated 95% confidence intervals (CI) were calculated for each 0.5% of the stance phase of the jump-landing task for . Group ensemble mean and 95% CI values were plotted graphically using Microsoft Excel (Version 15; Microsoft Corporation, Redmond, WA). Statistical significance for a movement profile *group main effect* pre-HTL was defined as any portion of the stance phase when the 95% CI's for the *poor* and *excellent* groups did not overlap (McKeon et al. 2009; Kuenze et al. 2014). A significant change pre- to post-HTL or *time main effect* was defined as any portion of the stance phase when the 95% change score CI did not envelope zero. A *group-by-time change magnitude interaction effect* was defined as a period during the stance phase when one group's change waveform 95% CI was above or below zero during the stance phase and the other group's change waveform 95% CI enveloped zero

throughout 100% stance. A *group-by-time change duration interaction effect* was defined as a scenario in which both groups experienced a time main effect for the same biomechanical variable but there was at least a 5% difference in duration of the time main effect between groups.

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CHAPTER 4

PARTICIPANT DEMOGRAPHICS

A total of 45 participants out of 157 demographically eligible participants screened into the study, meeting all movement and aerobic power inclusion criteria. However, two participants who screened into the *poor* group could not complete the controlled acute HTL protocol, thus a total of 43 participants (N=43; *excellent* (n=22), *poor* (n=21)) were included in the final study sample. Participant anthropometrics and fitness demographic data are presented in table 4.1 below. Independent samples *t*-tests revealed there was no significant ($P>0.05$) differences between the *poor* and *excellent* movement groups for any demographic or fitness variable.

	Excellent (n=22)	Poor (n=21)
Age (years)	20.5 (1.9)	20.4 (1.3)
Height (m)	1.44 (0.44)	1.63 (0.23)
Mass (kg)	64.5 (7.8)	60.9 (6.1)
Resting Heart Rate (bpm)	65.0 (9.8)	71.5 (14.5)
Resting Diastolic Blood Pressure (mmHg)	73.7 (9.6)	74.3 (14.2)
Resting Systolic Blood Pressure (mmHg)	112.9 (6.4)	115.2 (7.4)
100% Ventilatory Threshold ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	33.2 (4.2)	34.0 (4.1)
110% Ventilatory Threshold ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	36.5 (4.6)	37.3 (4.5)
120% Ventilatory Threshold ($\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$)	39.8 (5.0)	40.7 (4.9)

Table 4.1 - Group Demographic & Fitness Level Descriptive Statistics: Group Means & (SDs)

Acute High Training Load Exposure Protocol

Movement profile group means, standard deviations, and 95% confidence intervals are reported in table 4.2 below. The results of the 2×5 mixed model ANOVA analyses revealed there was no significant ($P>0.05$) group-by-time (exercise stage) interaction or any group main effects. There was a significant main effect of exercise stage for RER, RPE, heart rate and VO_2 ; with a significant increase between stage #1 and all other stages (figure 4.1) in both groups ($P<0.05$) primarily driven by the difference in initial metabolic activity in response to exercise onset (Brooks 1985) between stage #1 and the remaining stages

Collectively our HTL metabolic and perception data suggest this novel acute HTL protocol acted as a significant mechanism of control within our study, effectively exposing participants to the same relative training load and associated metabolic demands. While this acute HTL protocol was developed specifically for this study, our results support its use in future research when the intent is to expose individuals to relatively identical training stimuli in order to isolate the effects of various independent variables that are hypothesized to moderate an individual's response to a controlled training stress.

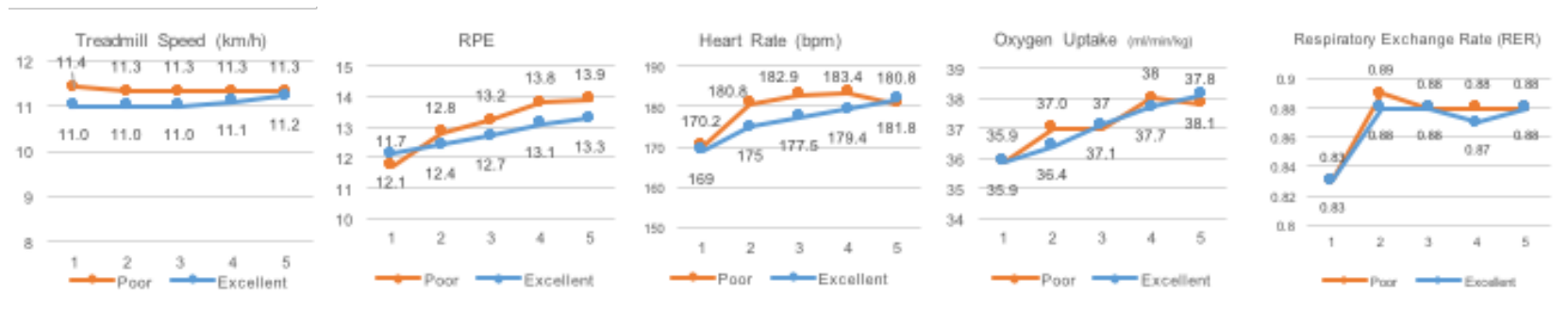


Figure 4.1 – Acute HLT protocol speed, perceptual measures (RPE) and associated metabolic responses (Heart Rate, Oxygen Uptake, RER).

Table 4.2 Controlled Acute High Training Load Exposure Stage Metabolic & Intensity Perception Data

Mean (SD) [95% CI]	Stage 1		Stage 2		Stage 3		Stage 4		Stage 5	
	Excellent	Poor	Excellent	Poor	Excellent	Poor	Excellent	Poor	Excellent	Poor
Treadmill Speed (km•h ⁻¹)	11.0 (1.1) [10.6, 11.5]	11.4 (1.0) [10.9, 11.9]	11.0 (1.2) [10.5, 11.6]	11.3 (1.0) [10.8, 11.8]	11.0 (1.2) [10.5, 11.5]	11.3 (1.0) [10.8, 11.7]	11.1 (1.2) [10.6, 11.6]	11.3 (1.1) [10.8, 11.8]	11.2 (1.1) [10.7, 11.7]	11.3 (1.1) [10.8, 11.8]
Rate of Perceived Exertion (Borg 6-20)	12.1 (0.6) [11.5, 12.6]	11.7 (1.7) [11.3, 12.5]	12.4 (1.0) [11.8, 12.9]	12.8 (1.6) [12.2, 13.4]	12.7 (0.9) [12.1, 13.2]	13.2 (1.5) [12.6, 13.7]	13.1 (1.1) [12.5, 13.8]	13.8 (1.6) [13.2, 14.2]	13.3 (1.2) [12.7, 13.9]	13.9 (1.4) [13.3, 14.5]
Heart Rate (bpm)	169.0 (12.9) [161.9, 176.8]	170.2 (19.6) [162.9, 177.4]	175.0 (15.1) [169.1, 180.8]	180.8 (11.8) [174.8, 186.8]	177.5 (14.0) [172.3, 182.7]	182.9 (9.6) [177.6, 188.2]	179.4 (14.6) [174.2, 184.7]	183.4 (9.2) [178.0, 188.8]	181.8 (11.7) [176.2, 187.4]	180.8 (14.2) [175.0, 186.5]
Oxygen Uptake (ml•kg ⁻¹ •min ⁻¹)	35.9 (3.2) [34.4, 37.5]	35.9 (3.9) [34.4, 37.6]	36.4 (4.4) [34.7, 38.3]	37.0 (4.1) [35.1, 38.9]	37.1 (3.8) [35.5, 38.6]	37.0 (3.4) [35.4, 38.6]	37.7 (4.0) [36.0, 39.5]	38.0 (3.9) [36.2, 39.7]	38.1 (3.6) [36.5, 39.6]	37.8 (3.6) [36.2, 39.4]
Respiratory Exchange Ratio (RER)	0.83 (0.03) [0.81, 0.84]	0.83 (0.04) [0.82, 0.85]	0.88 (0.04) [0.87, 0.90]	0.89 (0.03) [0.87, 0.90]	0.88 (0.04) [0.87, 0.89]	0.88 (0.03) [0.87, 0.90]	0.87 (0.03) [0.86, 0.90]	0.88 (0.03) [0.86, 0.89]	0.88 (0.04) [0.86, 0.89]	0.88 (0.03) [0.87, 0.90]

Table 4.2 – Controlled acute high training load exposure stage metabolic & intensity perception data

AIM #1 – Evaluate the effects of movement quality on MSK tissue stress biomarkers at rest and in response to an acute HTL.

We observed movement profile to have a strong influence on the response of CK-MM to an acute HTL exposure. Individuals with an *excellent* movement profile exhibit a greater release of CK-MM into circulation 30 minutes after acute HTL exposure compared to their counterparts with *poor* movement quality. Furthermore, our results do not support the role of movement profile to influence baseline or post-HTL cartilage stress responses in healthy, physically active college-aged females. However, our results suggest healthy physically active college-aged females experience similar increases in COMP levels compared to their male counterparts when isolating investigation to those who are responders, exhibiting ~37% increases in COMP after acute HTL exposure.

Group mean-by-time % Δ , baseline and post HTL raw unit (ng/ml) and natural log transformed concentration values of systemic and musculoskeletal tissue stress biomarkers for the *poor* and *excellent* groups are presented in table 4.3 along with the associated group-by-time standard deviations, 95% confidence intervals, and effect size calculations between movement profiles at each time point. Sample means and descriptive statistics collapsed across movement profile groups for the main effect of time are reported in table 4.3. Mixed-model ANOVA analyses did not identify a significant group-by-time interaction effect for any of the biomarkers ($P>0.05$). However, upon closer analysis of the group-by-time CK-MM means and their associated 95% confidence intervals, it appears there is substantial separation between the *poor* group's upper, and the *excellent* group's lower bounds for both the the log-transformed and raw post HTL concentration values, with a moderate-to-large effect size (table 4.3, figure 4.2 (a)). Furthermore, the *excellent* group exhibited a significantly greater % Δ for CK-MM ($P<0.05$)

compared to the *poor* group, thus implicating a greater average within-subject CK-MM elevation in response to the HTL in the *excellent* group, that may not be accounted for with the general linear model ANOVA (Dijkers 2013; Fitzmaurice, Laird, and Ware 2011).

In addition to a greater CK-MM elevation in response to acute HTL, there was a significant main effect for group on CK-MM, with the *excellent* group having greater overall CK-MM relative to the *poor* group ($P < 0.05$).

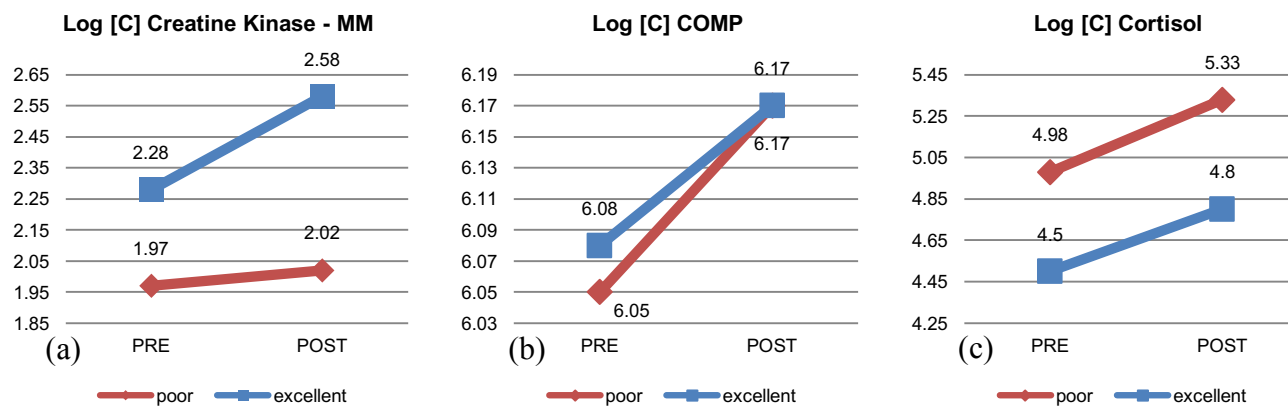


Figure 4.2 – Log [C] of values and acute HTL response behavior of CK-MM (a), COMP (b), and cortisol (c).

Table 4.3 - Group-by-time Raw (ng/ml), Natural Logarithm-transformed, & %Δ serum biomarker concentrations pre and post acute HTL.

Table 4.5 - Group-by-time Raw (ng/ml), Natural Logarithm-transformed, & %Δ serum biomarker concentrations pre and post acute H1N1.							
	Excellent			Poor			Cohen's D
	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI	
CORTISOL^{A,c}							
Pre Log [C]	19	4.5 (0.31)	[4.37, 4.64]	21	4.98 (0.41)	[4.8, 5.16]	1.32
Post Log [C]*	19	4.8 (0.72)	[4.48, 5.12]	21	5.33 (0.72)	[5.02, 5.64]	0.74
Pre Raw [C] (ng/ml)	19	96.62 (30.49)	[82.91, 110.32]	21	157.64 (65.49)	[129.63, 185.66]	1.19
Post Raw [C] (ng/ml)*	19	161.22 (144.55)	[96.23, 226.22]	21	252.52 (140.26)	[192.53, 312.51]	0.64
%Δ Raw [C]	19	59.99 (120.35)	[5.87, 114.11]	21	68.4 (91.22)	[29.39, 107.42]	0.08
CK-MM^{A,d}							
Pre Log [C]	21	2.28 (0.87)	[1.91, 2.66]	18	1.97 (0.17)	[1.89, 2.05]	0.50
Post Log [C]*	21	2.58 (0.9)	[2.19, 2.96]	18	2.02 (0.24)	[1.91, 2.13]	0.85
Pre Raw [C] (ng/ml)	21	14.88 (16.99)	[7.62, 22.15]	18	7.26 (1.33)	[6.64, 7.87]	0.63
Post Raw [C] (ng/ml)*	21	20.14 (23.26)	[10.19, 30.09]	18	7.73 (2.01)	[6.81, 8.66]	0.75
%Δ Raw [C]	21	68.62 (115.61)	[19.18, 118.07]	18	7.12 (22.4)	[-3.23, 17.47]	0.74
COMP^c							
Pre Log [C]	21	6.08 (0.26)	[5.97, 6.19]	20	6.05 (0.4)	[5.88, 6.23]	0.09
Post Log [C]**	21	6.17 (0.33)	[6.03, 6.31]	20	6.17 (0.39)	[5.99, 6.34]	0.01
Pre Raw [C] (ng/ml)	21	453.15 (121.01)	[401.4, 504.91]	20	461.12 (195.11)	[375.61, 546.63]	0.05
Post Raw [C] (ng/ml)**	21	502.5 (162.48)	[433.01, 572]	20	512.03 (201.85)	[423.57, 600.49]	0.05
%Δ Raw [C]	21	12.15 (27.83)	[0.24, 24.05]	20	18.45 (44.73)	[-1.15, 38.06]	0.17

^asignificant for group × time interaction

^bPOST-30 sample

^csignificant for group

^dPOST-0 sample

^esignificant for time

^fsignificant change score difference

Table 4.3 – Group-by-time Raw (ng/ml), natural logarithm-transformed, & %Δ serum biomarker concentrations per and post-acute HTL

AIM #2 – Investigate the influence of movement quality on systemic stress biomarkers at rest and in response to an HTL.

There were significant main effects for group ($P < 0.05$) and time ($P < 0.05$) on cortisol (table 4.3, figure 4.2 (c)). Interestingly, while the *poor* and *excellent* group's respective pre and post HTL cortisol values and associated 95% confidence intervals remained separated at each time point. There was substantial overlap in the *poor* group's pre HTL and *excellent* group's post HTL cortisol 95% confidence intervals. Within the context of the main effects for group and time on cortisol, these results recognize the *poor* group to have exhibited a resting cortisol level that is similar to the *excellent* group's post HTL cortisol levels. Furthermore, there were no significant associations between movement quality profile and responder-type for any of the biomarkers ($P > 0.05$).

AIM #3 – Determine if movement quality moderates biomechanical responses to an acute HTL.

All pre HTL, change, and post HTL waveform data are presented in figures 4.3-4.7. A significant change pre- to post-HTL or *time main effect* was defined as any portion of the stance phase when the 95% change score CI did not envelope zero. A *group-by-time change magnitude interaction effect* was defined as a period during the stance phase when one group's change waveform 95% CI was above or below zero during the stance phase and the other group's change waveform 95% CI enveloped zero throughout 100% stance. A *group-by-time change duration interaction effect* was defined as a scenario in which both groups experienced a time main effect for the same biomechanical variable but there was at least a 5% difference in duration of the time main effect between groups.

Summarized time main effects, magnitude interactions, and duration interactions are described under each change waveform for ease of interpretation. Additionally, table 4.3 provides a summary of pre, post, and each group's change responses relative to acute HTL exposure.

In summary, the *poor* group experienced nine significant biomechanical adaptations in response to HTL, whereas the *excellent* group only experienced three significant changes in their movement profile from pre to post HTL. Specifically, the *poor* group went on to adopt a movement profile associated with higher mechanical loads after acute HTL exposure. The *poor* group experienced decreases in sagittal plane trunk and hip flexion motion, as well as a greater duration decrease in knee flexion motion compared to the *excellent* group. Furthermore, the *poor* group exhibited significant increases in internal knee extension, knee varus, and hip abduction braking moments during early stance. Collectively, the *poor* group's biomechanical response to the acute HTL resulted in a greater overall force exposure, as they experienced greater duration elevations in VGRF>1 body weight as well prolonged increases in proximal ATSF compared to the *excellent* group.

Table 4.4 - Summary of pre, post and biomechanical variable change response relative to acute HTL exposure.

VARIABLE	Pre-High-Intensity Exercise Exposure		Change Behavior		Post-High-Intensity Exercise Exposure	
	finding	temporal interval (stance)	finding	temporal interval (stance)	finding	temporal interval (stance)
Thorax Flexion Angle (WLD)	Excellent > Poor	40%-95%	Excellent ↔ Poor ↓	- 0-40%	Excellent > Poor	41%-100%
Thorax Frontal Plane Euler Angle (WLD)	Poor = Excellent	-	Excellent ↔ Poor ↔	- -	Poor = Excellent	-
Hip Flexion Angle (EULER)	Excellent > Poor	26%-87%	Excellent ↔ Poor ↓	- 0%-30%	Excellent > Poor	8%-90%
Hip Abduction Angle (EULER)	Excellent > Poor	5%-84%	Excellent ↓ Poor ↔	0%-8% -	Excellent > Poor	22%-52%
Hip Extension Moment	1) Poor > Excellent (Marginal Separation) 2) Excellent > Poor (Marginal Separation)	1) @~3% 2) 95%-100%	Excellent ↔ 1) Poor ↓ 2) Poor ↓	- 1) 7%-10% 2) 90%-98%	Excellent > Poor	95%-100%
Hip Flexion Moment	Excellent > Poor	70%-87%	Excellent ↔ Poor ↔	- -	Poor = Excellent	-
Hip Abduction Moment	Poor > Excellent	20%-80%	Excellent ↑ 1) Poor ↓ 2) Poor ↑	1%-10%, 15%-22%, 65%-92% 1) 2%-4% 2) 12%-15%	Poor > Excellent	30%-80%
Knee Flexion Angle (EULER)	Excellent > Poor	5%-95%	Excellent ↓ Poor ↓	0%-12% 0%-48%	Excellent > Poor	5%-95%
Knee Valgus Angle (EULER)	Poor > Excellent	2%-5%, 22%-32%, 38%-73%	Excellent ↑ Poor ↔	0%-5%, 90%-100% -	Poor > Excellent	25%-62%
Knee Valgus Angle (SEGMENT)	Poor > Excellent	0%-98%	Excellent ↑ Poor ↔	0%-6% -	Poor > Excellent	2%-80%
Medial Knee Displacement	Poor > Excellent	10%-80%	Excellent ↔ Poor ↓	- 5%-8%	Poor > Excellent	10%-68%
Knee Extension Moment	1) Poor > Excellent 2) Excellent > Poor	1) 12% -15%, 55-75% 2) 90 -98%	Excellent ↓ Poor ↓	0%-2%, 10%-15% 5%-15%	1) Poor > Excellent 2) Excellent > Poor	1) 2%-4%, 18%-28%, 55%-76% 2) 90%-98%
Knee Varus Moment	Poor > Excellent	22%-68%	Excellent ↔ Poor ↑	- 3%-5%	Poor > Excellent	25%-55%
Knee Valgus Moment	Excellent > Poor	22%-68%	Excellent ↑ Poor ↑	6%-8% 90%-95%	Excellent > Poor	25%-55%
Vertical Ground Reaction Force	1) Poor > Excellent 2) Excellent > Poor	1) 6%-12%, 18%-81% 2) 95%-100%	1) Excellent ↑ 2) Excellent ↓ 1) Poor ↓ 2) Poor ↑	1) 75%-87% 2) 95%-98% 1) 0%-2%, 5%-8% 2) 43%-87%	1) Poor > Excellent 2) Excellent > Poor	1) 12%-38%, 50%-81% 2) 95%-100%
Anterior Tibial Shear Force	1) Poor > Excellent 2) Excellent > Poor	1) 12%-15%, 25%-32%, 52%-75% 2) 85%-98%	1) Excellent ↓ 2) Excellent ↑ 1) Poor ↓ 2) Poor ↑	1) 6%-8%, 95%-98% 2) 78%-85% 1) 5%-8%, 90%-98% 2) 50%-76%	1) Poor > Excellent 2) Excellent > Poor	1) 2%-3%, 11%-34%, 50%-76% 2) 85%-98%

Table 4.4 - Summary of pre, post and biomechanical variable change response relative to acute HTL exposure.

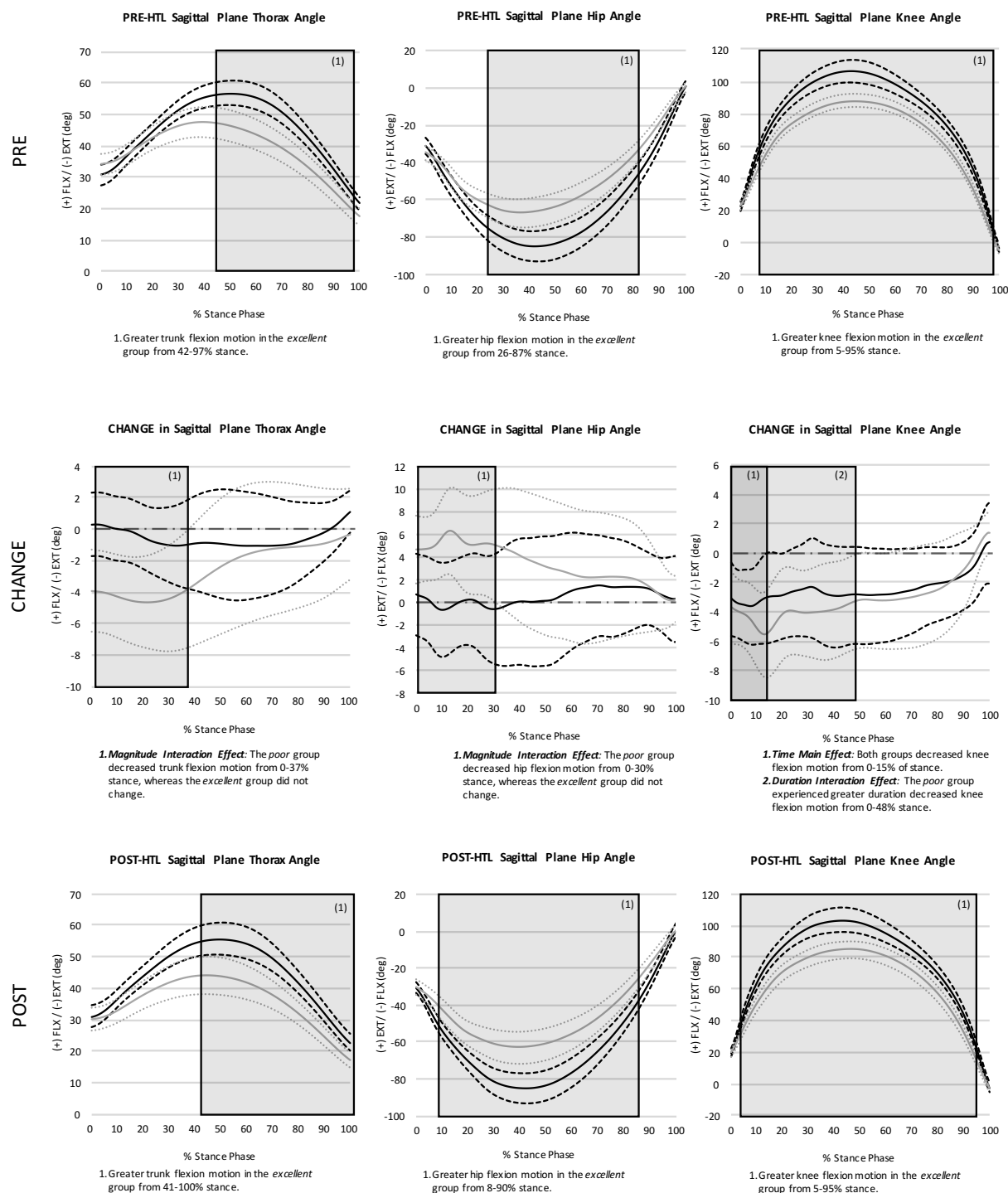


Figure 4.3 – Sagittal plane trunk, hip, and knee motion group ensemble curves and associated 95% confidence interval waveforms over the stance phase of the jump-landing task.

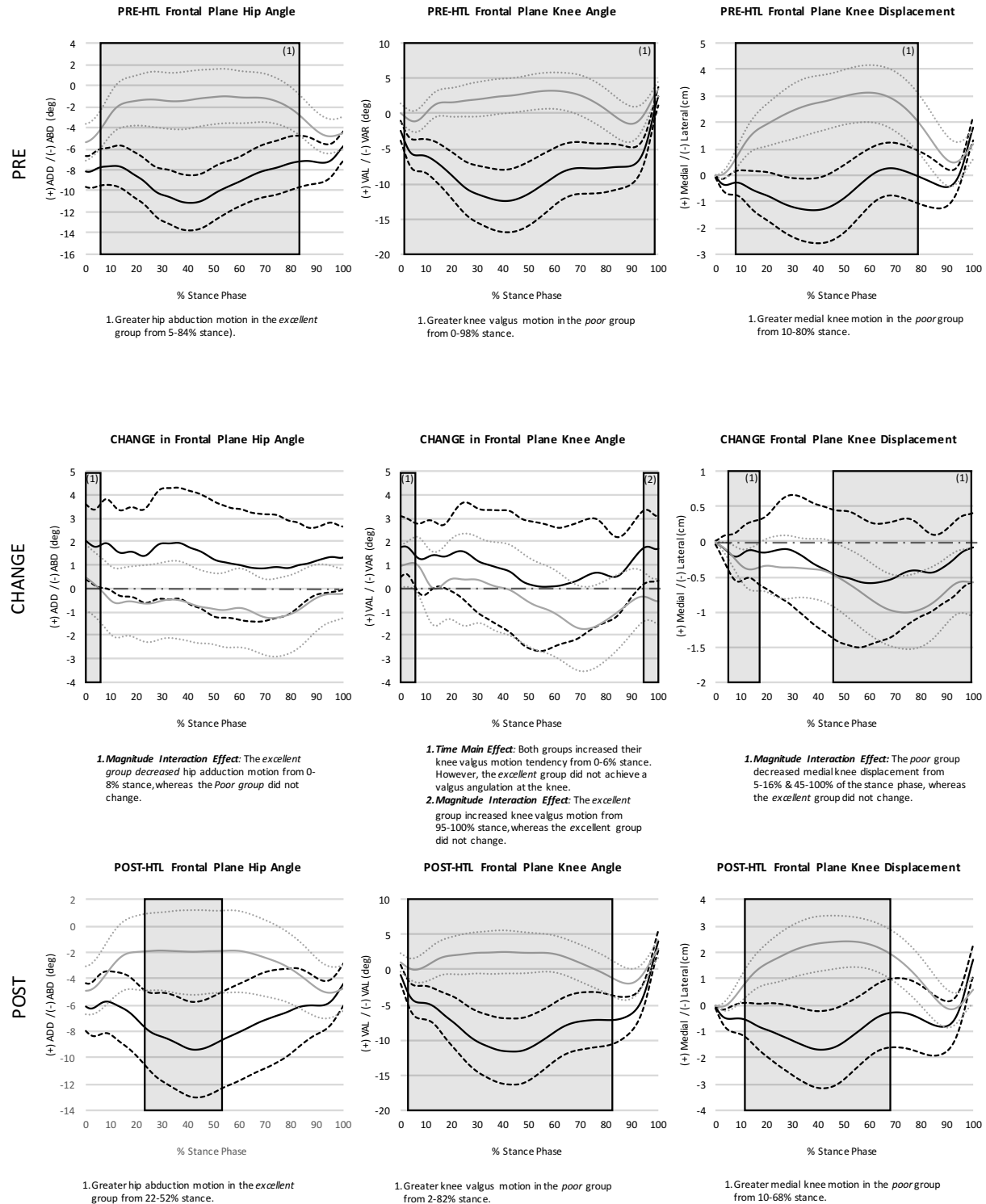


Figure 4.4 – Frontal plane hip and knee motion group ensemble curves and associated 95% confidence interval waveforms over the stance phase of the jump-landing task.

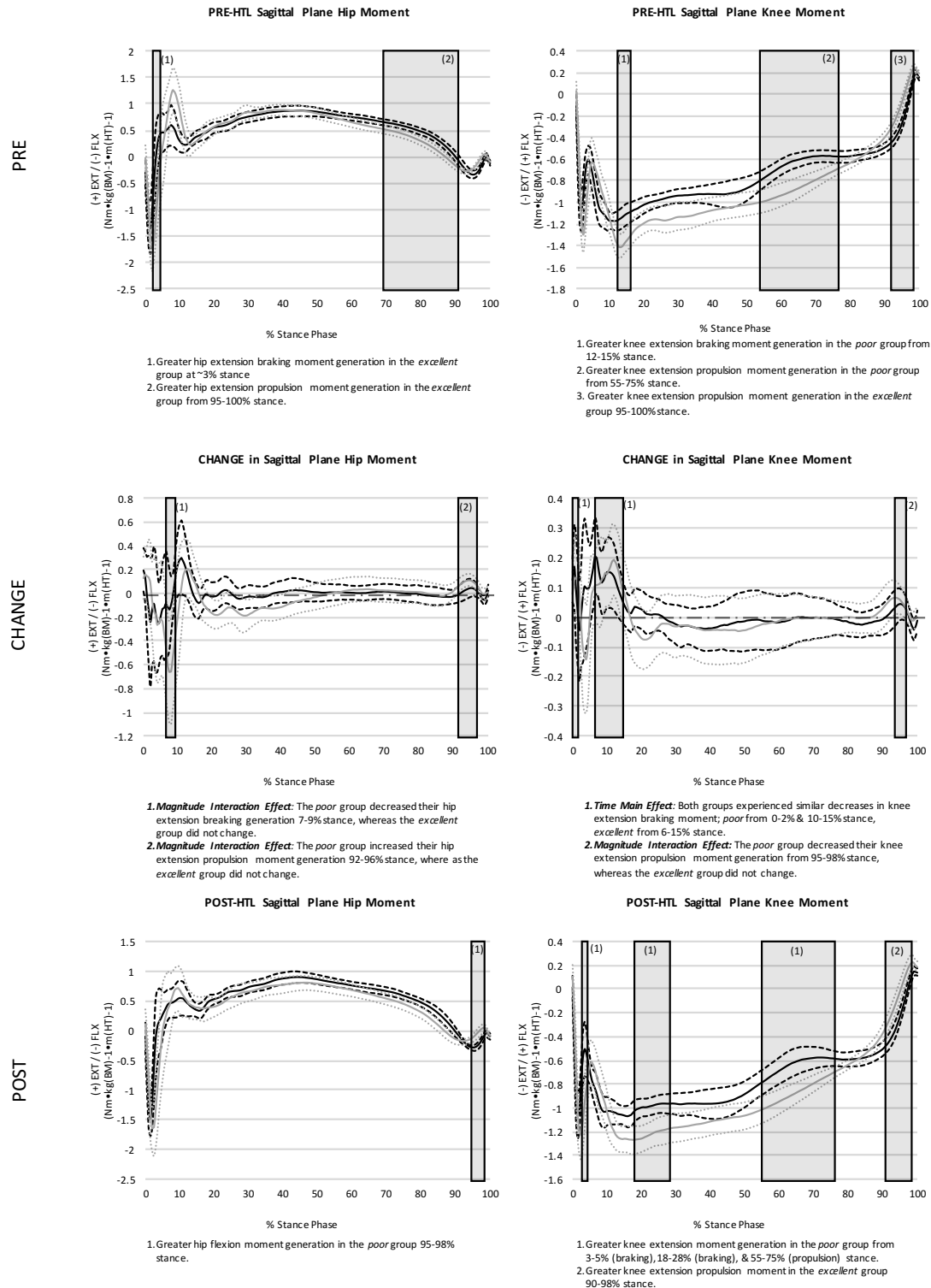


Figure 4.5 – Sagittal plane net internal hip and knee moment group ensemble curves and associated 95% confidence interval waveforms over the stance phase of the jump-landing task.

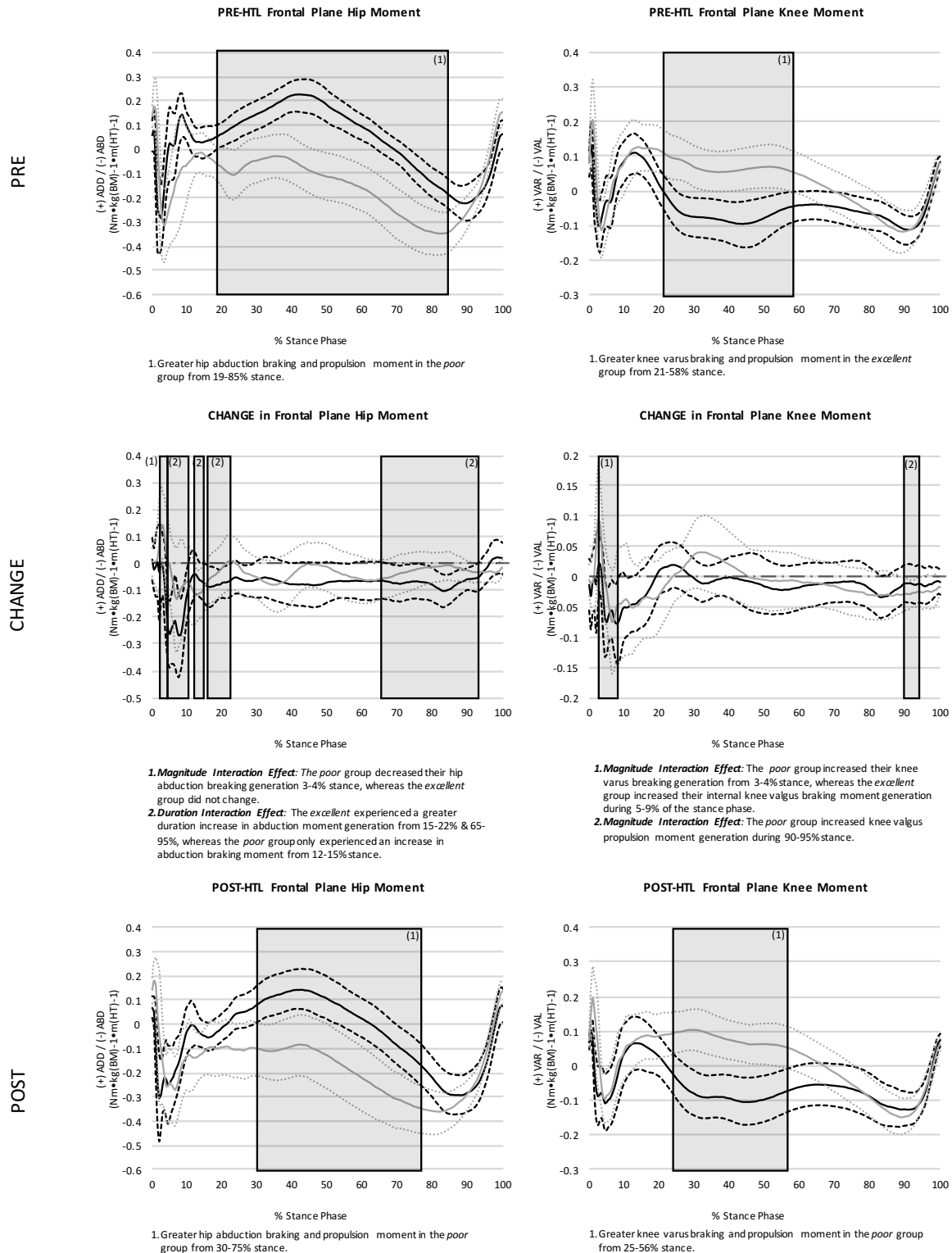


Figure 4.6 – Frontal plane net internal hip and knee moment group ensemble curves and associated 95% confidence interval waveforms over the stance phase of the jump-landing task.

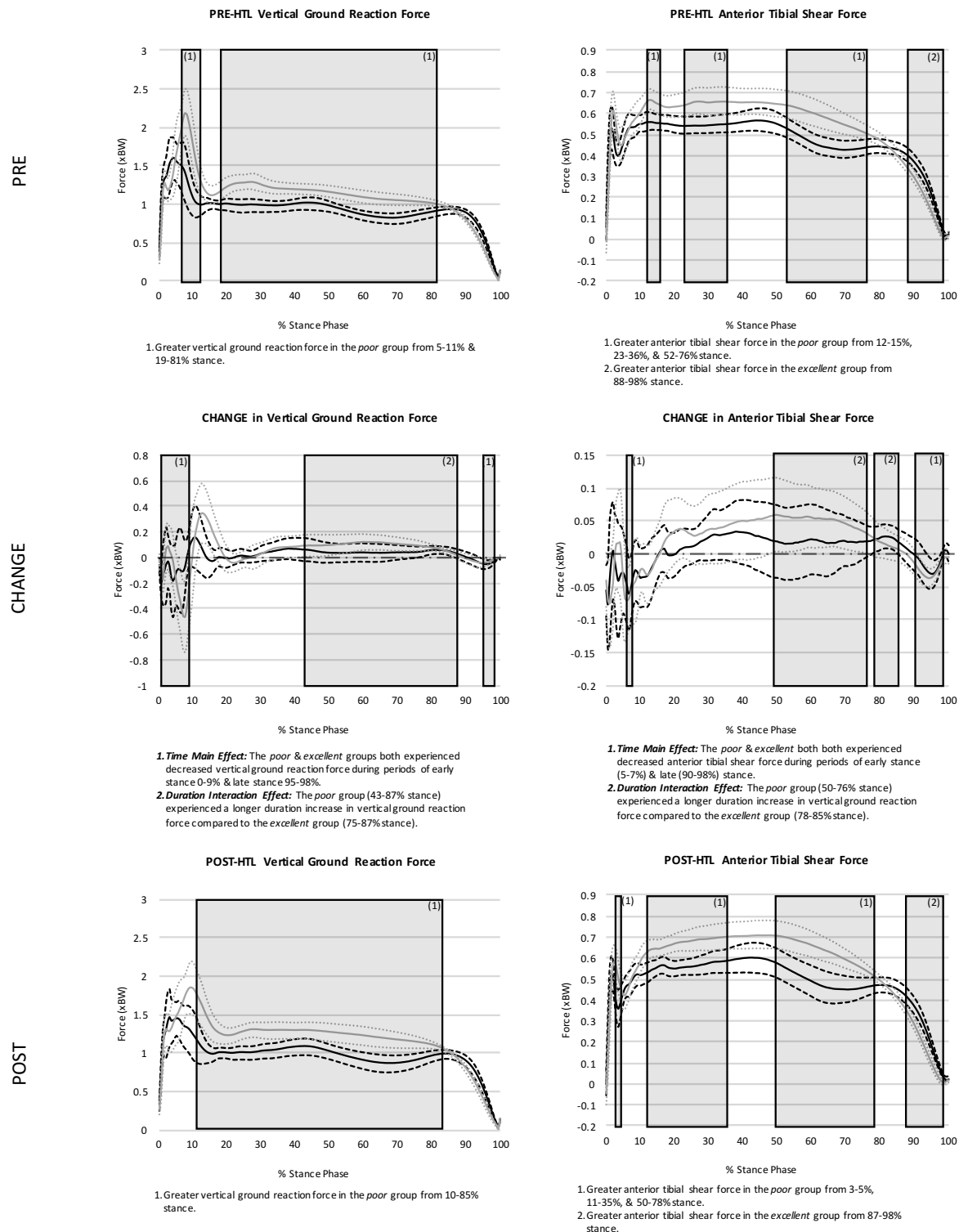


Figure 4.7 – Vertical ground reaction force (VGRF) and anterior tibial shear force (ATSF) group ensemble curves and associated 95% confidence interval waveforms over the stance phase of the jump-landing task.

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CHAPTER 5: MANUSCRIPT #1

Movement Quality Impacts Biomechanical Resilience to Acute High Training Load Exposure in Physically Active Young-Adult Females

Overview

Background: “Stiff” landing biomechanics and excessive frontal plane knee motion, such as limited trunk, hip, and knee flexion and medial knee displacement have been identified as risk factors or movement patterns associated with lower extremity musculoskeletal injury and elevated joint loads. High-intensity work or high training loads have been observed to induce biomechanical changes associated with the above high-load movement profile. However, the influence of an individual’s baseline movement quality profile on their resilience to high training load-induced degradation in their biomechanics has not yet been explored.

Aim: Investigate the influence of an individual’s inherent baseline movement profile on their biomechanical response to an acute bout of intensive training load exposure.

Methods: 43 physically active, healthy, college-aged females were enrolled in this study and were assigned to a *poor* high-load or *excellent* low-load movement profile group operationally defined by the Landing Error Scoring System (LESS). Jump-landing 3D biomechanics were evaluated prior to and following a metabolically controlled acute high training load exercise protocol (HTL). Continuous change-score waveforms and their associated 95% confidence intervals were constructed for the *poor* and *excellent* movement profile groups. Portions of the change score waveforms not enveloping zero within the 95% confidence intervals were

identified as significant biomechanical responses to HTL. Significant biomechanical responses to HTLs were qualitatively compared between the *poor* and the *excellent* groups based on the magnitude, duration, and direction of the identified biomechanical change.

Results: The *poor* group experienced nine significant biomechanical adaptations in response to HTL, whereas the *excellent* group only experienced three significant changes in their movement profile from pre to post HTL. Specifically, the *poor* group went on to adopt a movement profile associated with higher mechanical loads after acute HTL exposure.

Conclusions: Movement quality profile influences the physically active, healthy, college-aged female's biomechanical response to HTLs associated with sport participation. The *excellent* movement quality profile appears to be more biomechanically resilient to acute HTL. Thus, promoting an *excellent* movement profile in individuals partaking in exercise activity with HTLs may reduce their propensity to adopt movement strategies associated with high-mechanical loading and lower extremity musculoskeletal injury.

INTRODUCTION

Musculoskeletal (MSK) injuries during sport and physical activity are common,(Conn, Annett, and Gilchrist 2003) costly,(Jacobs 2008; Woolf and Pfleger 2003) and have long-term health consequences,(Lohmander et al. 2007; Maffulli et al. 2010) representing a substantial socioeconomic burden.(Cumps et al. 2008) Injury severity is the primary determinant of an injury's cost to society.(van Mechelen 1997) Individuals who sustain a high-severity sport-related MSK injury such as an anterior cruciate ligament (ACL) rupture experience sizeable direct and indirect medical costs, acute and long-term decreases in productivity that result in a reduction in human capital, and decrease quality of life.(Cumps et al. 2008; van Mechelen 1997) Thus, there is a considerable need to understand underlying factors that may contribute to MSK injury during sport and physical activity to reduce the socioeconomic burden of MSK injury and maximize the health benefits of sport and physical activity participation.

The current body of evidence has identified lower extremity biomechanics to be both risk factors(D. A. Padua et al. 2015; Cameron, Peck, and Owens 2014; Dai et al. 2012) and mechanisms(Krosshaug et al., 2007; Shimokochi & Shultz, 2008) for sport-related MSK injury, such as non-contact ACL rupture. Interestingly, 50% to 70% of sport-related ACL injuries are reported to be the result of a noncontact mechanism of injury(Agel, Arendt, and Bershadsky 2005; B P Boden et al. 2000; Mihata, Beutler, and Boden 2006) Noncontact mechanisms causing sport-related ACL rupture are described as “forces applied to the knee at the time of injury that result from an athlete's own movement that did not involve contact with another athlete or object”. (Marshall, Padua, & McGrath, n.d.) Thus, biomechanics are associated with an individual's prospective risk for sport-related MSK injury, and are readily identifiable during injury events.

In addition to an individual's biomechanical profile, current evidence also links fatigue(Galambos, Terry, Moyle, Locke, & Lane, 2005) and high training loads(Gabbett, 2004; Gabbett & Jenkins, 2011) to increased MSK injury rates. The influence of fatigue and high training loads on MSK injury may be linked to alterations in biomechanics as previous research indicates that fatigue leads to maladaptive changes in lower extremity biomechanics associated with noncontact ACL injury(Quammen et al., 2012; Santamaria & Webster, 2010; SCHMITZ et al., 2014; Webster, Santamaria, McClelland, & Feller, 2012)

Clinical movement assessments such as The Landing Error Scoring System (LESS) can be used as a reliable and valid clinical tool to discriminate between individuals with *excellent* and *poor* movement quality profiles.(Padua et al., 2009) “Stiff” sagittal plane landing biomechanics and excessive medial knee displacement movement patterns are commonly associated with *poor* movement quality, and are linked to numerous lower extremity injuries, including ACL rupture,(Walden et al. 2015) patellofemoral pain syndrome,(Elias et al., 2004; Mizuno et al., 2001) medial collateral ligament injury,(Hull, Berns, Varma, & Patterson, 1996) lower-leg stress fracture,(Cameron, Peck, & Owens, 2014) as well as the progression of knee osteoarthritis (OA).(Brouwer et al., 2007; Sharma et al., 2001) It is possible that an interaction exists between an individual's movement quality profile and their response to hard training loads. Specifically, those with poor movement quality may experience greater overall loading during training, thus undergo a maladaptive biomechanical response. To our knowledge, research has not examined the potential interaction between an individual's movement quality profile and response to a fatiguing bout of acute HTL.

The primary purpose of this study was to better understand the ramifications of an individual's inherent baseline movement profile on their biomechanical response to an acute bout

of intensive training load in healthy, physically active college-aged females, a population at high risk of severe lower extremity MSK injury.(Hootman, Dick, and Agel 2007; Arendt, Agel, and Dick 1999) Previous studies have identified limited sagittal plane trunk, hip, and knee motion and excessive frontal plane knee and hip motion to be associated with non-contact severe injury mechanism, specifically ACL rupture.(Krosshaug et al. 2007; Sheehan, Sipprell, and Boden 2012) We hypothesize that individuals with a low-load, sagittal plane dominant, *excellent* movement profile will exhibit greater resistance against the adoption of non-sagittal plane landing biomechanics and subsequent high-loads associated with lower extremity MSK injury after an acute ITL. Conversely, following an acute ITL, individuals with a high-load, “stiff” sagittal plane and uncontrolled frontal plane landing biomechanics will adopt movement strategies such as decreases in trunk, hip, and knee flexion motion associated with higher lower extremity loading and injury.

METHODS

Participants

This study employed a two-group, cross-sectional, repeated measures design to investigate the influence of *poor* and *excellent* movement profiles on biomechanical changes in response to HTL (Figure 5.1). Participants were recruited from the female student body at The University of North Carolina at Chapel Hill. Participants were demographically eligible if they had a history of participating in at least the high-school varsity-level of soccer, basketball, rugby, lacrosse, and team handball, tennis, track and field, volleyball, or field hockey. Specifically, eligible participants were 18 – 25 years of age, actively participating in at least 30 minutes of moderate to high-intensity physical activity a minimum of three days per week. Participants were

ineligible for participation if they had history of lower extremity surgery within the past year, lower extremity joint surgery, prior ACL or meniscal injury, lower extremity injury in the past six months that prevented participation in physical activities for more than 3 consecutive days, neuroendocrine, neurological, or metabolic disease or condition, or dysmenorrhea or amenorrhea within the past 6 months.

Demographically eligible participants were enrolled in this study if they demonstrated a operationally defined *poor* or *excellent* baseline movement profile during a LESS assessment described by Padua et al. (D. A. Padua et al. 2009). Enrolled participants also needed to achieve an estimated maximal oxygen uptake ranging from 40 – 50 ml•kg⁻¹•min⁻¹ via submaximal aerobic power assessment described below. The selected aerobic power range is representative of a “good to superior” aerobic fitness level within the population (Medicine, 2009), and coincides with the representative of the college female field and court sport athlete’s aerobic power (Enemark-Miller, Seegmiller, and Rana 2009). A total of 45 participants out of 157 demographically eligible participants screened into the study, meeting all movement and aerobic power inclusion criteria. However, two participants who screened into the *poor* group could not complete the controlled HTL protocol, thus a total of 43 participants (N=43; *excellent* (n=22), *poor* (n=21)) were included in the final study sample. A priori power analysis of previously published data revealed that a total sample size of 40 participants (*poor* (n=20) & *excellent* (n=20)) would allow the investigators to detect a minimum 20% change in biomechanical dependent variables from pre- to post-HTL, with a power of at least 0.80 and $\alpha=0.05$. Previous studies using repeated measures designs have observed HTL to have a moderate (Cohen’s $d=0.55$) to large (Cohen’s $d=2.2$) effect on sagittal and frontal plane LPHC and knee

biomechanics linked to ACL injury(Chappell et al., 2005; McLean et al., 2007; Cortes et al., 2012; Quammen et al., 2012; Liederbach et al., 2014).

Procedures

All procedures were conducted after institutional review board (IRB) approval. Informed consent was obtained prior to initiation of the study protocol outlined in figure 5.2. Enrolled participants reported to the laboratory for a single-testing session. Prior to the 3D biomechanical assessment and HTL, participants provided a urine sample for evaluation of hydration level using the specific gravity technique via refractometry (TS Meter, American Optical Corp., Keene, New Hampshire, USA) to ensure adequate hydration (urine specific gravity ≤ 1.02) prior to exercise.(Stuempfle and Drury 2003) Height (cm) and mass (kg) were measured and recorded using stadiometer and a digital scale (Detecto 2381, Detecto, Webb City, Missouri, USA).

Participant Preparation

Participants donned non-reflective spandex shorts and a sports bra. The principal investigator (BF) secured rigid clusters of retroreflective markers on the participant's dominant lower extremity (side subject identified they would use to kick a soccer ball for maximum distance) at the dorsal surface of the shod foot, midpoint of the anterolateral shank, midpoint of the anterolateral thigh, and sacrum using double-sided tape and athletic pre-wrap. After the rigid clusters were secured, the principal investigator attached individual retroreflective markers to the dominant limb's medial and lateral ankle malleoli, femoral condyles, bilateral anterior superior iliac spines, and bilateral acromion processes.

Three-Dimensional Motion Analysis

A ten-camera motion capture system (Vicon Bonita 10, Vicon Motion Systems, Los Angeles, CA, USA) interfaced with a force plate (Type 4060-10, Bertec Corporation, Columbus, OH, USA) centered within a 2×2×2 meter capture volume was used to sample three-dimensional (3D) marker trajectories (200 Hz) and ground reaction force (1,000 Hz) data using Vicon Nexus v1.7.1 motion capture software (Vicon Motion Systems, Los Angeles, CA, USA). World and segment axis systems were established by a right hand three-dimensional Cartesian coordinate system. The positive *x*-axis was designated forward/anterior, the positive *y*-axis to the left, and the positive *z*-axis upward/superiorly relative to the participant.(B. Frank et al. 2013)

A static trial was collected with the participant facing the positive *x*-axis of the world coordinate system. Hip joint centers were estimated using the Bell method.(A. L. Bell, Pedersen, and Brand 1990) Knee and ankle joint centers were estimated as the midpoint between the medial and lateral femoral epicondyles and malleoli, respectively. The flexion/extension axis of the knee was defined using the transepicondylar axis established between the medial and lateral femoral epicondyle markers from the static calibration trial for each subject.(Wu et al. 2002) The trunk segment was modeled as a rigid body defined proximally by the bilateral acromion process markers and distally by the sacrum cluster flexing and extending about the world medial-lateral axis (*y*-axis).(B. Frank et al. 2013) Markers were removed from the medial and lateral epicondyles, ankle malleoli, and bilateral anterior superior iliac spines after the static trial.

Pre-HTL Jump-Landing Assessment

Participants stood atop a 30 cm box placed 50% their body height from the leading edge of the two conductive force plates. Synonymous with the LESS protocol described by Padua et

al.,(D. A. Padua et al. 2009) the principal investigator instructed the participant to “*face forward, and jump down to the center of the force plates, and rebound upward for a maximal vertical jump*” with the right foot landing on the right force plate and the left foot atop the left force plate. During the jump-landing task instruction emphasis on starting the jump in a neutral positioning with toes pointing forward, feet shoulder-width apart, and both feet leaving the box at the same time was communicated to the participant to promote a successful trial execution. All participants completed three practice trials to re-familiarize themselves with the jump-landing task. Following the three practice trials, the participant completed three trials of the jump-landing task used for 3D motion analysis of the pre-HTL jump-landing task.

Ventilatory Threshold Assessment

For determination of ventilatory threshold, participants completed a speed-only graded submaximal aerobic capacity assessment(Vanhoy 2012; Berry et al. 2016) on a motorized treadmill (GE T2100 Exercise Stress System, General Electric – Healthcare, Little Chalfont, UK) with measurement of respiratory gas exchange using a metabolic cart (TrueOne 2400 Metabolic Measurement System, Parvo Medics, Sandy, Utah, USA) and instantaneous monitoring of heart rate (A39 Exercise Monitor, Under Armour Inc., Baltimore, Maryland, USA). Prior to the ventilatory threshold assessment, the principal investigator completed standard calibration procedures of the flow, carbon dioxide, and oxygen sensors of the metabolic cart using a 3.0 L syringe of known gases. The principal investigator described the ventilatory threshold assessment protocol to the participant before the initiation of the evaluation procedures (Figure 5.2).

After the principal investigator delivered testing instructions and explained the assessment procedures, the participant's resting heart rate (Under Armour A39, Under Armour Inc., Baltimore, Maryland, USA), blood pressure (ADC 700 Diagnostix® Series Pocket Aneroid Sphygmomanometer, American Diagnostics Corporation, Hauppauge, New York, USA; 3MTMLittmann® Stethoscope, 3M, St. Paul, Minnesota, USA), were measured and recorded after sitting for five minutes. The principal investigator then reviewed the participant's resting vital signs to ensure there is no evidence of contraindications to participation in a submaximal exercise.(Medicine, 2009)

After the principal investigator ensured there were no contraindications to exercise participation, the ventilatory threshold assessment protocol outlined in figure 5.2 was initiated. Following completion of the ventilatory threshold assessment, the participant's ventilatory threshold was determined using a modified V-slope method(Sue et al. 1988) (APPENDIX 3) to identify when there was an observed increase in ventilatory equivalent for oxygen without an accompanying increase in the ventilatory equivalent for carbon dioxide(Davis, Whipp, and Wasserman 1980) in the participant's respiratory gas exchange data sampled during the assessment protocol. The VO_2 and treadmill speed coincident with 100%, 110%, and 120% were identified and used to define the control of the treadmill running speed during the HTL protocol (figure 5.2.)

Controlled High-Intensity Exercise Exposure (HTL)

The controlled HTL protocol deployed in this study was novel (figure 5.2). Previously described HTL protocols lack rigorous control of intensity to compare dependent variables between movement profile groups. Thus the internal load(Foster et al. 2001) the study

participants experience may be variable based on fitness level and other confounding individual physiological variables.(Foster et al. 2001) The aim of this study's HTL protocol was to expose participants to approximately identical internal training loads based on their individualized ventilatory threshold. Controlling the HTL intensity using this novel approach implied individuals used similar energy systems,(Hopker, Jobson, and Pandit 2011) and experienced the same relative exercise intensity based on their individual system physiology.(Davis, Whipp, and Wasserman 1980; Hopker, Jobson, and Pandit 2011) During the HTL, the treadmill speed was increased or decreased by $0.161 \text{ km}\cdot\text{h}^{-1}$ increments to maintain an individualized instantaneous VO_2 coincident with 100 – 120% ventilatory threshold, RER between 0.85 – 0.95, and RPE 12 – 15. At end of each minute of each stage (5 stages, 5 minutes) of the HTL protocol treadmill speed, RPE, VO_2 , and RER were recorded and entered into a Microsoft Excel spreadsheet (Version 15; Microsoft Corporation, Redmond, WA). The stringent control of relative exercise intensity across subjects and between groups permitted isolated identification of the effects of an individual's movement profile on their biomechanical response to a uniform metabolic stress exposure.(Hopker, Jobson, and Pandit 2011)

Post-HTL Jump-Landing Assessment

Immediately following the HTL protocol the principal investigator expediently secured retroreflective markers as described previously. After a static trial was collected to establish a viable 3D biomechanical model the participants completed two sets of ten “booster exercise” jump-landings separated by 30 seconds of rest to offset recovery that may have occurred during marker attachment. Following the “booster exercise,” the participants completed three additional trials of the jump-landing task to evaluate post-HTL jump-landing 3D biomechanics.

Data Reduction & Analysis

All kinematic and kinetic data were imported into The Motion Monitor v9.0 software system (Innovative Sports Training, Inc., Chicago, IL, USA) to calculate joint angles, internal joint moments, and ground reaction force vector components. Kinematic data were filtered using a 4th order low pass Butterworth filter at 20 Hz.(Yu et al. 1999). Net internal joint moments were derived using an inverse dynamics procedure, representative of the combined influence of soft tissue forces acting about a joint.(Gagnon and Gagnon 1992; Winter 2009) Data were then exported and reduced using a customized software program to calculate the dependent variables of interest (Matlab v2016b, The Mathworks, Inc., Natick, MA, USA). Sagittal plane trunk motion was calculated as the trunk segment relative to the world axis system. Dominant limb hip joint motion was defined as motion of the thigh segment relative to the pelvis segment using a Cardan angle sequence of Y ((+) extension/(-) flexion), X' ((+) adduction/(-) abduction). Dominant limb knee joint motion was defined as the motion of the shank segment relative to the thigh segment using a Cardan angle rotation sequence of Y ((+) flexion/(-) extension).(Wu et al. 2002) Frontal plane knee motion was defined by as a combined segment angles of the thigh and the shank segments rotation relative to the world x -axis ((+) valgus (or tibial abduction)/(-) valgus (tibial adduction)) to avoid avoid multi-planar cross talk that occurs with excessive medial knee displacement.(B. Frank, Blackburn, and Padua 2013) Medial knee motion (displacement) was calculated as the difference between the instantaneous value of the y -axis position of the center of the knee joint and the y -axis position of the knee joint center at initial contact with respect to the world axis system.(D. R. Bell et al. 2013) Proximal ATSF was calculated as the net anteriorly directed shearing component of the force acting at the knee joint along the proximal tibia's x -axis.(Chappell et al. 2005) Vertical ground reaction force was

calculated as the pure vertical component of the ground reaction force vector coincident with the world z-axis.

All biomechanical data were calculated during the stance phase of the jump-landing task defined as the point of initial ground contact to toe-off. Initial ground contact was defined as the first time point the vertical ground reaction force exceeded 10N. Toe-off was defined as the first time point from initial ground contact that the vertical ground reaction force was than 10N.(D. A. Padua et al. 2009)

All biomechanical data were analyzed as continuous normalized waveforms during the stance phase of the jump-landing.(Kuenze et al. 2014) Kinematic and kinetic data were normalized to 201 data points (knots) over the stance phases of the three jump-landing task trials using a cubic spline function. Previous studies have described the stance phase duration to range from 190 to 374 milliseconds during jump-landing tasks.(Cowley et al. 2006; Strutzenberger et al. 2014) Thus, use of 201 knots derived from 1,000 Hz raw and interpolated kinetic and kinematic data points provided sufficient resolution of biomechanical variables of interest during the jump-landing task. Each knot was calculated as the mean value of the respective derived knots from each of the three jump-landing tasks (eq. 1) (trial 1, trial 2, trial 3).

$$Knot_{i...201} = \frac{Knot_{i\ t1} + Knot_{i\ t2} + Knot_{i\ t3}}{3}$$

(eq. 1)

To calculate changes in biomechanical variables from baseline to post-exercise, the differences between the respective individual baseline and post-HIE knot values ($knot_{bi}$ & $knot_{fi}$) was calculated to form a 201 knot waveform reflecting the change in the biomechanical variable of interest (eq. 2).

$$Knot_{\Delta i...201} = Knot_{fi} - Knot_{bi}$$

(eq. 2)

Change score waveforms were calculated for all biomechanical variables of interest, representative of the participant's biomechanical response to HTL.

Statistical Analysis

Demographic and ventilatory threshold data were compared between groups using independent samples *t*-tests. Separate repeated measures (2×5) ANOVAs were used to compare the average treadmill speed, RPE, VO₂, and RER for each five-minute stage between groups during the controlled HTL protocol.

Pre-HTL, post-HTL, and change score frontal and sagittal plane kinematic and kinetic variable ensemble means and associated 95% confidence intervals (CI) were calculated for each 0.5% of the stance phase of the jump-landing task for . Group ensemble mean and 95% CI values were plotted graphically using Microsoft Excel (Version 15; Microsoft Corporation, Redmond, WA). Statistical significance for a movement profile *group main effect* pre-HTL was defined as any portion of the stance phase when the 95% CI's for the *poor* and *excellent* groups did not overlap.(McKeon et al. 2009; Kuenze et al. 2014). A significant change pre- to post-HTL or *time main effect* was defined as any portion of the stance phase when the 95% change score CI did not envelope zero. A *group-by-time change magnitude interaction effect* was defined a as a period during the stance phase when one group's change waveform 95% CI was above or below zero during the stance phase and the other group's change waveform 95% CI enveloped zero throughout 100% stance. A *group-by-time change duration interaction effect* was defined as a scenario in which both groups experienced a time main effect for the same biomechanical

variable but there was at least a 5% difference in duration of the time main effect between groups.

RESULTS

Participants Demographic

Participant anthropometrics and fitness demographic data are presented in table 1.1. Independent samples *t*-tests revealed there was no significant ($P < 0.05$) differences between the movement groups for any demographic variable.

Controlled High-Intensity Exercise Exposure Metabolics & Perceived Intensity

Movement profile group means, standard deviations, and 95% confidence intervals are reported in table 1.2. Repeated measures ANOVA analyses revealed there was no significant ($P > 0.05$) group-by-exercise stage interaction or any group main effects. There was a significant time main effect for RER, RPE, heart rate and VO_2 ; with a significant increase over time in both groups ($P < 0.05$).

Biomechanics

All pre HTL, change, and post HTL waveform data are presented in figures 5.3-5.7. Summarized time main effects, magnitude interactions, and duration interactions are described under each change waveform for ease of interpretation. The *poor* group experienced nine significant biomechanical adaptations in response to HTL, whereas the *excellent* group only experienced three significant changes in their movement profile from pre to post HTL

DISCUSSION

The most important finding of this study is that an individual's movement quality profile moderates their biomechanical response to an acute HTL. Participants with *poor* movement quality underwent decreased trunk and hip flexion motion, as well as increased internal knee varus braking moment during a jump-landing task after acute HTL exposure. No such changes were observed in those with *good* movement quality. Furthermore, following the acute HTL we observed the *poor* group to experience increased VGRF and ATSF with concomitant decreases in knee flexion angle and hip abduction braking moment over a greater duration of the stance phase. In contrast, those with an *excellent* movement profile displayed greater resilience by displaying fewer biomechanical alterations after acute HTL exposure. The results of this study suggest that a *poor* baseline movement quality promotes biomechanical alterations associated with non-contact ACL injury and loading (Walden et al. 2015; T E Hewett, Torg, and Boden 2009; Koga et al. 2010; Krosshaug et al. 2007) (Markolf et al. 1995; Withrow et al. 2006; Sheehan, Sipprell, and Boden 2012; Barry P Boden et al. 2010) in response to acute HTL; however, this is not the case in those with *excellent* movement quality.

To our knowledge this is the first study to compare biomechanical responses following acute HTL between those with *excellent* and *poor* movement profiles. Previous research has identified fatigue to induce biomechanical changes associated with lower extremity injury (Santamaria and Webster 2010; Cortes et al. 2012; Quammen et al. 2012; Schmitz et al. 2014; Borotikar et al. 2008); however, this work has focused on comparing the biomechanical response to fatiguing exercise in healthy (Cortes et al. 2012; Quammen et al. 2012; Chappell et al. 2005; B. S. Frank et al. 2014; Schmitz et al. 2014) or previously injured groups. (Webster et al. 2012; B. S. Frank et al. 2014) Both groups experienced transient decreases in VGRF, knee extension

braking moment, and ATSF during early stance, and similar brief decreases in propulsive VGRF during late stance. The literature is conflicted regarding influence of fatigue exposure or acute HTL on VGRF. Interestingly, previous studies have observed increases(Chappell et al. 2005; Dominguese, Seegmiller, and Krause 2012), decreases(Santamaria and Webster 2010; Schmitz et al. 2014), and no significant change(Cortes et al. 2012; B. S. Frank et al. 2014) in peak VGRF during the early stance phase of landing tasks following fatigue or acute HTL protocols. Thus, there is no consensus regarding early landing force changes in response to fatigue or acute HTL exposure. Interestingly, our findings of reduced VGRF, ATSF and internal knee extension moment following acute HTL in both groups are aligned with the results of studies deploying similar acute HTL protocols that incorporate periods of intermittent running and plyometric activities.(Quammen et al. 2012; Schmitz et al. 2014) These findings suggest that baseline movement profile does not moderate changes in these variables following acute HTL.

While the changes VGRF, ATSF and knee extension moment magnitude following acute HTL were similar between groups this was not the case for internal knee varus moment or trunk and hip flexion motion magnitudes. The poor movement quality group displayed increased internal knee varus moment combined with decreased trunk and hip flexion motion following acute HTL. Internal knee varus moment is analogous to external knee valgus moment, which has been shown to increase ACL loading and is associated with the prospective risk of ACL injury.(Timothy E Hewett et al. 2005) Lack of trunk motion control(Zazulak et al. 2007) and a more erect and upright body posture(Sheehan, Sipprell, and Boden 2012; T E Hewett, Torg, and Boden 2009) are also associated with ACL injury. Our findings indicate that *poor* movement quality subjects experienced significant changes in those variables that have been most strongly associated with ACL injury. Interestingly, no such changes were observed in the excellent

movement quality group. Thus, it appears that excellent movement quality subjects display greater resilience to change in those biomechanical variables associated with increased ACL injury risk following acute HTL, whereas the poor movement quality subjects experience a maladaptive change in these variables.

Further evidence of a maladaptive response to acute HTL in the poor movement quality subjects is seen in hip moment alterations. Specifically, the poor movement quality group demonstrated reduced internal hip extension and abduction moments during the early stance phase. In contrast, the excellent movement quality subjects increased internal hip abduction moment during early stance and experienced no alterations to internal hip extension moment. Internal hip abduction and extension moment during the early stance phase represents the braking response to control and limit hip adduction and flexion motion, respectively during the impact loading phase of jump-landing. Reduced internal hip abduction and extension moment following acute HTL suggests that those with poor movement quality may have less braking control of the corresponding motions during the impact loading phase of jump-landing. Overall, this may reduce the ability for dynamic hip stability in poor movement quality subjects following acute HTL.

Individuals in the *excellent* group exhibited greater “biomechanical resilience” following the acute HTL; with only small decreases in hip abduction and knee varus motion and a concurrent propensity to increase in internal hip abduction braking and propulsion moments post acute HTL (figure 5.1). More importantly, the excellent group did not experience changes in those variables most associated with ACL injury (trunk kinematics, hip kinematics, and frontal plane knee moment). Collectively, the results of this study indicate that an individual’s response to acute HTL is mediated by their baseline movement quality profile. Specifically, those with

poor movement quality undergo greater loading and altered trunk and hip kinematics in response to acute HTL, which may increase their risk of injury. In contrast, individuals with *excellent* movement quality exhibit greater biomechanical resilience to acute HTL, safeguarding athletes against the biomechanical maladaptation associated with higher inert tissue loading conditions (BEYNNON and FLEMING 1998) and potential lower extremity injury.(Dai et al. 2012)

We believe that differences in the biomechanical response to acute HTL between groups are largely influenced by differences in movement quality at baseline. Individuals in the *poor* group completed a jump-landing task with less trunk, hip, and knee flexion, hip abduction, and greater knee valgus and medial knee motion resulting in a “stiff” sagittal plane and elevated frontal plane lower extremity motion profile linked to knee injury.(Krosshaug et al. 2007; Walden et al. 2015; Sheehan, Sipprell, and Boden 2012) The *poor* group’s “stiffer” landing profile was observed to elicit significantly greater loading across the lower extremity. Specifically, at baseline the *poor* group experienced $\sim 0.2 \text{ Nm} \cdot \text{kg}_{(\text{BW})}^{-1} \cdot \text{m}_{(\text{HT})}^{-1}$ greater internal knee extension and $\sim 0.1 \text{ Nm} \cdot \text{kg}_{(\text{BW})}^{-1} \cdot \text{m}_{(\text{HT})}^{-1}$ internal knee varus moments with resultant elevations in VGRF and ATSF equal to 80% and 13% body mass respectively. Additionally it should be noted that during the baseline jump-landings, the *poor* group was exposed to VGRF loads >1 body weight for over 80% of the entire stance phase. Whereas, the *excellent* group was only exposed to a VGRF load >1 body weight less than 20% of the stance phase. These findings suggest the *poor* group is exposed VGRF loads >1 body weight four times longer than the *excellent* group during the jump-landing task. Thus, both the magnitude and duration of high-load exposure is significantly greater in the *poor* group, resulting in greater repetitive MSK system load exposure in the *poor* group during the controlled HTL.

The current study design offers insight regarding the interaction between an individual's movement quality profile and response to acute training loads similar to the physical demands of sport. The LESS criteria used in the current study to group individuals into *poor* and *excellent* movement groups effectively discriminated between individuals with biomechanical profiles associated with high or low mechanical load exposure during the stance phase of a jump-landing task (figure 5.1).

The results of our study are in agreement with previous literature, suggesting that individuals with a *poor* movement profile exhibit biomechanics associated with inefficient load dissipation (M. F. Norcross et al. 2015; Powers 2010; Pollard, Sigward, and Powers 2010) and injury (D. A. Padua et al. 2015; Cameron, Peck, and Owens 2014; Powers 2010). Biomechanical resilience observed in the *excellent* group may be explained by their persistent efficiency in load attenuation maintained primarily within the sagittal plane during HTL compared to the *poor* group (Pollard, Sigward, and Powers 2010; Podraza and White 2010; Marc F. Norcross et al. 2013a; Marc F. Norcross et al. 2013b). Therefore the *poor* group was likely forced to undergo a greater change in their movement strategy to meet the physically demanding requirements of the controlled HTL.

Over time, the *poor* group may experience the cumulative detrimental effects of their inherently limited load attenuation efficiency (Marc F. Norcross et al. 2013a; Pollard, Sigward, and Powers 2010) owing to the observed resultant maladaptive biomechanical response in the current study. Thus, it is possible the *poor* group experiences a greater mechanical load exposure to their MSK system during a similar HTL (Tim J Gabbett and Ullah 2012; Franklyn-Miller et al. 2012) contributing to a higher biomechanical injury risk compared to their *excellent* group counterparts (D. A. Padua et al. 2015; Cameron, Peck, and Owens 2014).

The data from the ventilatory threshold assessment (table 1.) and controlled exercise protocol (table 2.) further implicate movement quality to be a primary factor driving the differences in biomechanical responses to an acute HTL. There was no significant group effect on ventilatory threshold, suggesting that both groups had similar fitness levels and metabolic profiles,(Sue et al. 1988; Davis, Whipp, and Wasserman 1980) eliminating any potential confounding effects of cardiovascular function and peripheral mechanisms of fatigue resistance to influence biomechanical responses to acute HTL exposure. Furthermore, there was no evidence of a group effect on any perceptual or metabolic measures during the HTL, thus the relative intensity of the exercise stress was similar in both groups. Moreover, the total work completed by both groups was similar, as there was no difference in treadmill speed between groups, suggesting both groups were exposed to the same external load(Halson 2014) during the HTL. Collectively, the homogeneity in fitness level, metabolic response, and imposed external load between groups further isolates the effects of baseline movement quality as a powerful modifier of the healthy female athlete's biomechanical changes secondary to acute HTL exposure.

The findings of this study support the clinical utility of the LESS as an economically effective movement assessment capable of describing both an individual's musculoskeletal injury risk(D. A. Padua et al. 2015; Cameron, Peck, and Owens 2014) and their probable biomechanical adaptations in response to HTL. Epidemiological evidence suggests that a majority of severe musculoskeletal injuries occur during higher intensity periods of training and competition secondary to underlying neuromuscular fatigue such as pre-season conditioning periods and post-season play.(Tim J. Gabbett 2004; T J Gabbett 2004; Hootman, Dick, and Agel 2007; Walden, Hagglund, and Ekstrand 2005) Therefore, clinicians should consider use of the

LESS to identify individuals who may be less biomechanically resilient during periods of high training intensity who may benefit from promotion of recovery management and behaviors.

Furthermore, the results of this study support the systematic implementation of injury prevention programs capable of improving an individual's movement profile.(DiStefano et al. 2011; Zebis et al. 2015; Myklebust et al. 2003; D. a. Padua and DiStefano 2009) Clinicians should consider the importance of promoting biomechanical resilience through the effective development of an athlete's *excellent* movement profile with injury prevention programming. This study is the first to suggest an athlete's inherent movement profile directly moderates self-imposed exposure to biomechanical loads associated with avoidable non-contact musculoskeletal injury during HTL. Thus, the results of this study provide foundational evidence that effective neuromuscular training programs aimed at developing an *excellent* movement profile(DiStefano et al. 2011; Zebis et al. 2015; Emery et al. 2015) may foster biomechanical resilience in athletes, reducing their susceptibility to adopt high-risk movement strategies during sport activity.

This study is not without limitations. The results of the current study lack generalization to other athlete demographics. Our results are limited to describing the biomechanical response profiles of healthy physically active college-aged females with a history of participation in field or court sports. While our results are not generalizable to the larger athlete and physically active population, college-aged female field and court sport athletes represent a population at highest risk of non-contact, severe lower extremity injury such as ACL rupture.(Hootman, Dick, and Agel 2007; Waldén et al. 2011; Peck et al. 2013)

Furthermore, we only evaluated the influence of baseline movement profile and HTL on biomechanical changes during a single sagittal plane dominant task. Changes in the landing biomechanics observed during the jump-landing cannot be generalized to more complex athletic

motions with greater multi-planar demands and changes in direction such as a sidestep cutting task. Currently there is a gap in the evidence-base highlighting jump-landing biomechanical profile transfer across tasks. However, previous literature has observed injury prevention programs aimed at increasing sagittal plane motion at the trunk hip and knee to result in changes in side-step cutting tasks,(DiStefano et al. 2011) suggesting there is potential for biomechanical resilience transfer across tasks.

Similarly, we did not evaluate biomechanical changes over the course of the HTL protocol and cannot implicate the same change trends in biomechanics were occurring during the HTL bout. However, the primary aim of this study was to determine the influence of movement profile on the biomechanical response to HTL in a jump-landing task directly predictive of injury risk. Differences in biomechanical changes during jogging gait have previously been reported between individuals with ACL reconstruction and healthy matched-controls.(Kuenze et al. 2014) Taken together with the results of our study it is recommended future investigations evaluate the effect of movement profile on real-time biomechanical adaptations during HTL to evaluate biomechanical resiliency during open tasks that may more closely resemble changes in sport activity outside of the laboratory environment.

In conclusion, the results of this study suggest that healthy female college-aged athletes with *excellent* movement profiles demonstrate greater biomechanical resilience upon HTL compared to their *poor* movement profile counterparts. Promoting greater biomechanical resilience through an *excellent* movement profile may reduce an individual's risk of injury when exposed to the high-intensity demands of sport and physical activity. Future research should investigate both the real-time influence of movement profile on biomechanical adaptations

during HTL, and the capacity of neuromuscular training programs to improve biomechanical resilience in individuals with pre-existing *poor* movement profiles.

NEW KEY FINDINGS

1. This study demonstrates for the first time that baseline movement profile influences biomechanical changes in response to HTL.
2. The LESS can be used as a clinical tool to identify individuals who experience maladaptive biomechanics in response to HTL.
3. Individuals with a *poor* / high-risk movement profile experience greater self-imposed mechanical load exposure secondary to their maladaptive biomechanical responses to HTL.

HOW MIGHT IT IMPACT CLINICAL PRACTICE IN THE FUTURE?

The proactive clinician should consider using the LESS to identify athletes with limited biomechanical resilience, targeting individuals with *poor* movement profiles as high-priority to receive corrective exercise / injury prevention programming to limit their mechanical load exposure and subsequent injury risk during sport participation.

Table 5.1 - Group Demographic Descriptive Statistics: Group Means & (SDs)

	Excellent	Poor
Age (years)	20.5 (1.9)	20.4 (1.3)
Height (m)	1.44 (0.44)	1.63 (0.23)
Mass (kg)	64.5 (7.8)	60.9 (6.1)
Resting Heart Rate (bpm)	65.0 (9.8)	71.5 (14.5)
Resting Diastolic Blood Pressure (mmHg)	73.7 (9.6)	74.3 (14.2)
Resting Systolic Blood Pressure (mmHg)	112.9 (6.4)	115.2 (7.4)
100% Ventilatory Threshold ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	33.2 (4.2)	34.0 (4.1)
110% Ventilatory Threshold ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	36.5 (4.6)	37.3 (4.5)
120% Ventilatory Threshold ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	39.8 (5.0)	40.7 (4.9)

Table 5.1 - Group Demographic Descriptive Statistics

Table 5.2 Controlled Acute High Training Load Exposure Stage Metabolic & Intensity Perception Data

Mean (SD) [95% CI]	Stage 1		Stage 2		Stage 3		Stage 4		Stage 5	
	Excellent	Poor	Excellent	Poor	Excellent	Poor	Excellent	Poor	Excellent	Poor
Treadmill Speed (km•h ⁻¹)	11.0 (1.1) [10.6, 11.5]	11.4 (1.0) [10.9, 11.9]	11.0 (1.2) [10.5, 11.6]	11.3 (1.0) [10.8, 11.8]	11.0 (1.2) [10.5, 11.5]	11.3 (1.0) [10.8, 11.7]	11.1 (1.2) [10.6, 11.6]	11.3 (1.1) [10.8, 11.8]	11.2 (1.1) [10.7, 11.7]	11.3 (1.1) [10.8, 11.8]
Rate of Perceived Exertion (Borg 6-20)	12.1 (0.6) [11.5, 12.6]	11.7 (1.7) [11.3, 12.5]	12.4 (1.0) [11.8, 12.9]	12.8 (1.6) [12.2, 13.4]	12.7 (0.9) [12.1, 13.2]	13.2 (1.5) [12.6, 13.7]	13.1 (1.1) [12.5, 13.8]	13.8 (1.6) [13.2, 14.2]	13.3 (1.2) [12.7, 13.9]	13.9 (1.4) [13.3, 14.5]
Heart Rate (bpm)	169.0 (12.9) [161.9, 176.8]	170.2 (19.6) [162.9, 177.4]	175.0 (15.1) [169.1, 180.8]	180.8 (11.8) [174.8, 186.8]	177.5 (14.0) [172.3, 182.7]	182.9 (9.6) [177.6, 188.2]	179.4 (14.6) [174.2, 184.7]	183.4 (9.2) [178.0, 188.8]	181.8 (11.7) [176.2, 187.4]	180.8 (14.2) [175.0, 186.5]
Oxygen Uptake (ml•kg ⁻¹ •min ⁻¹)	35.9 (3.2) [34.4, 37.5]	35.9 (3.9) [34.4, 37.6]	36.4 (4.4) [34.7, 38.3]	37.0 (4.1) [35.1, 38.9]	37.1 (3.8) [35.5, 38.6]	37.0 (3.4) [35.4, 38.6]	37.7 (4.0) [36.0, 39.5]	38.0 (3.9) [36.2, 39.7]	38.1 (3.6) [36.5, 39.6]	37.8 (3.6) [36.2, 39.4]
Respiratory Exchange Ratio (RER)	0.83 (0.03) [0.81, 0.84]	0.83 (0.04) [0.82, 0.85]	0.88 (0.04) [0.87, 0.90]	0.89 (0.03) [0.87, 0.90]	0.88 (0.04) [0.87, 0.89]	0.88 (0.03) [0.87, 0.90]	0.87 (0.03) [0.86, 0.90]	0.88 (0.03) [0.86, 0.89]	0.88 (0.04) [0.86, 0.89]	0.88 (0.03) [0.87, 0.90]

Table 5.2 - Controlled Acute High Training Load Exposure Stage Metabolic & Intensity Perception Measures

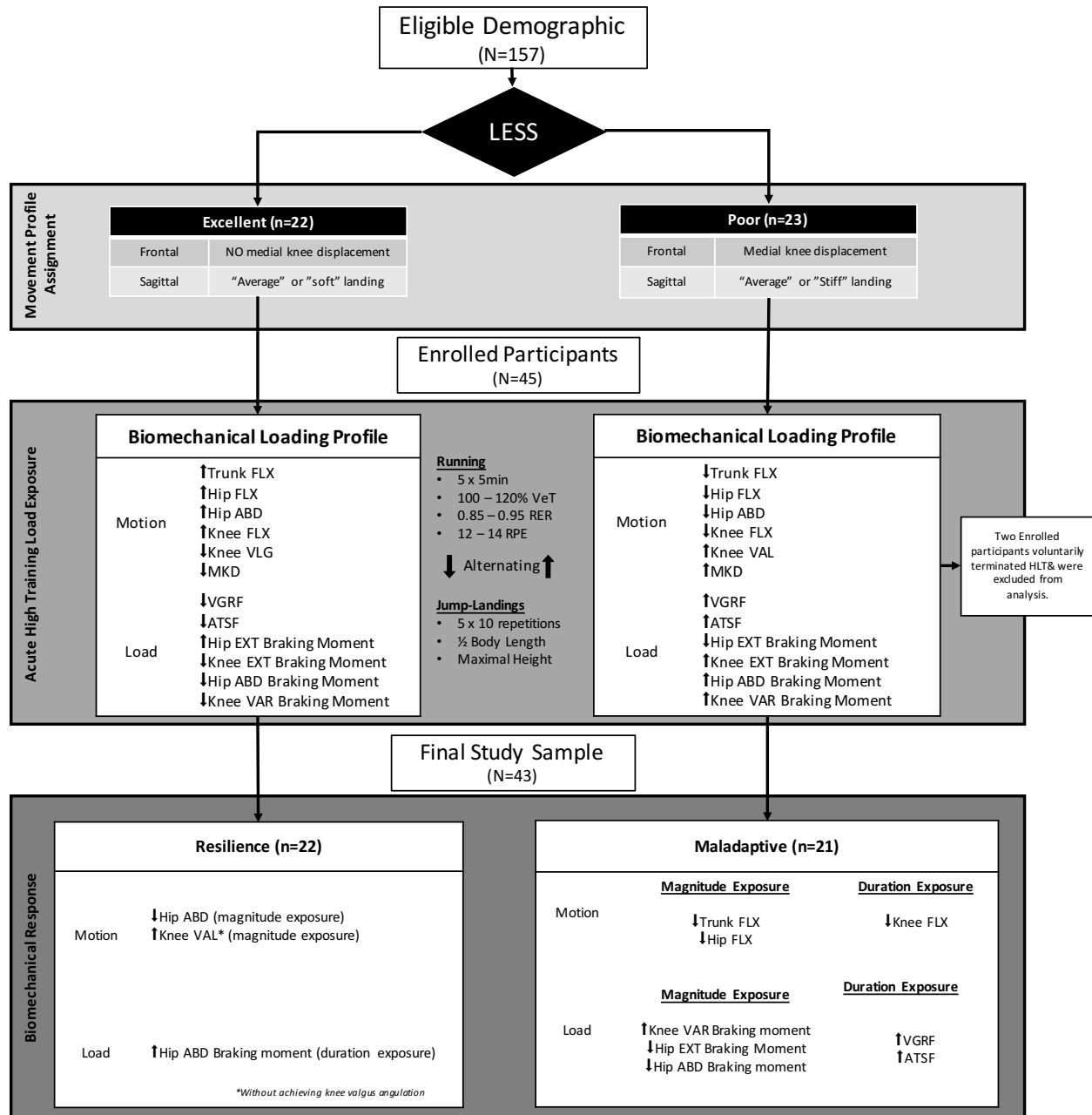


Figure 5.1 – Study Overview & Biomechanical Adaptations to acute High Training Load Exposure

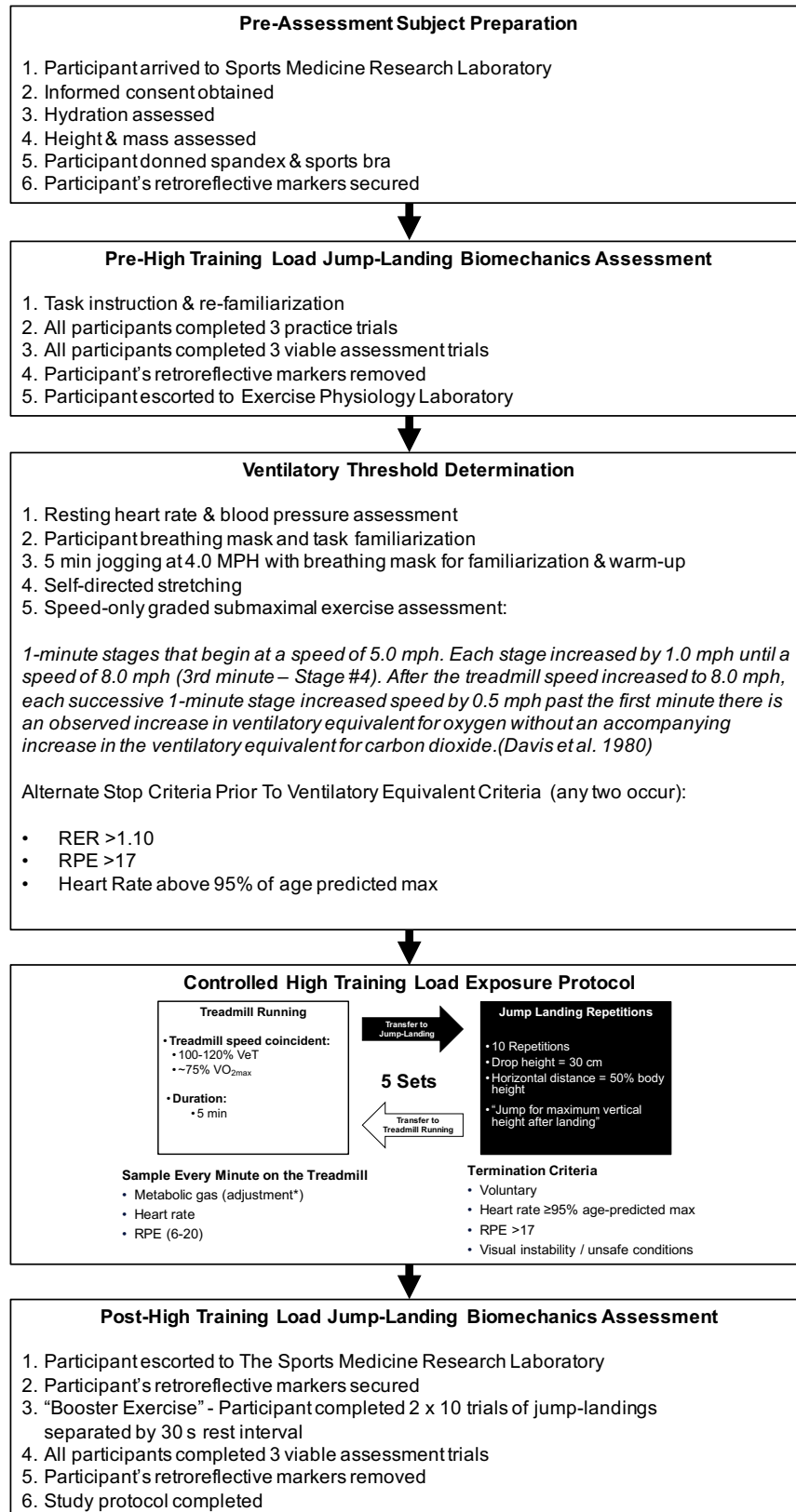


Figure 5.2 – Biomechanics Methodology Protocol

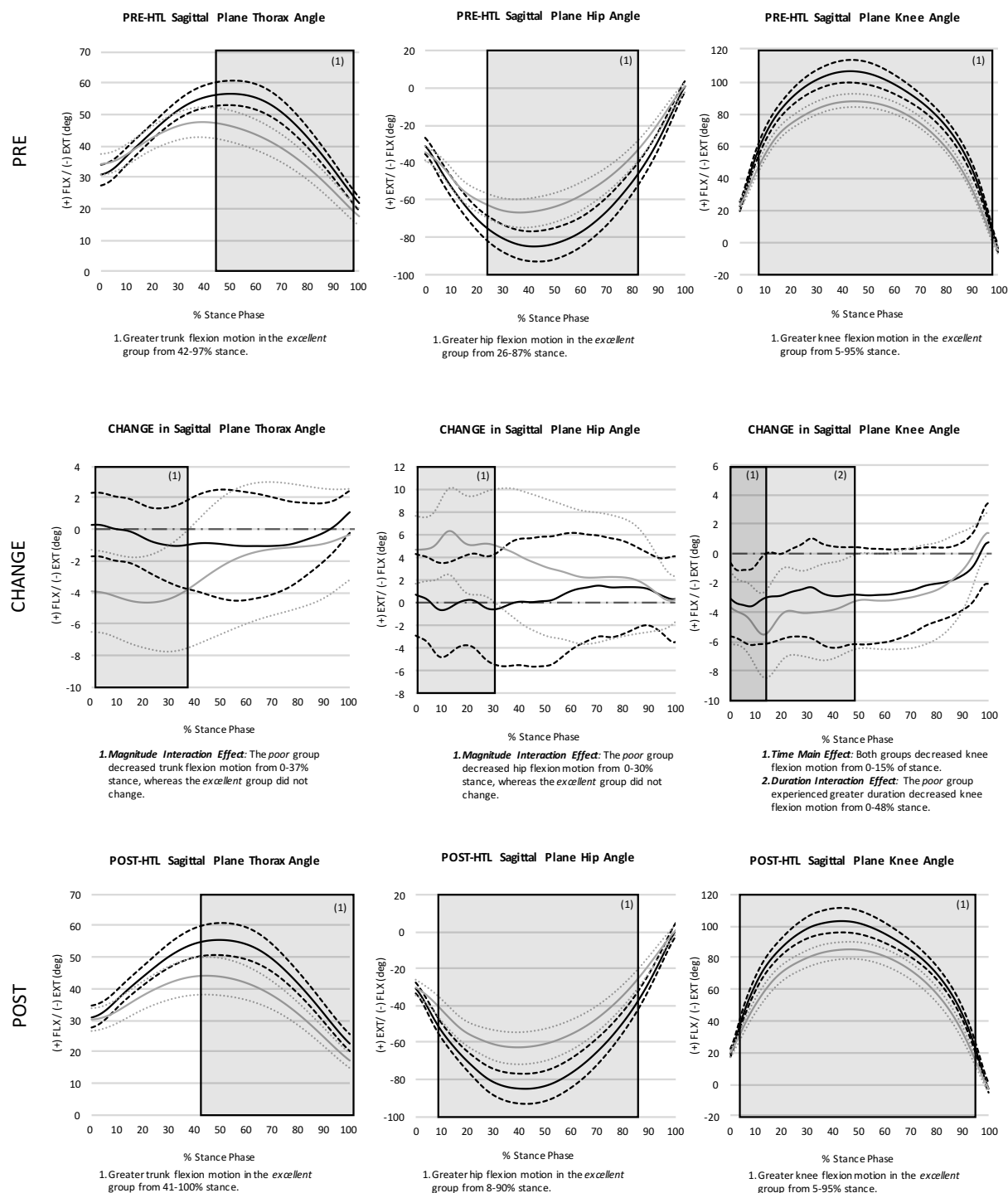


Figure 5.3 – Pre-HTL, Post-HTL, & Change Responses for Sagittal Plane Trunk, Hip, & Knee Kinematics

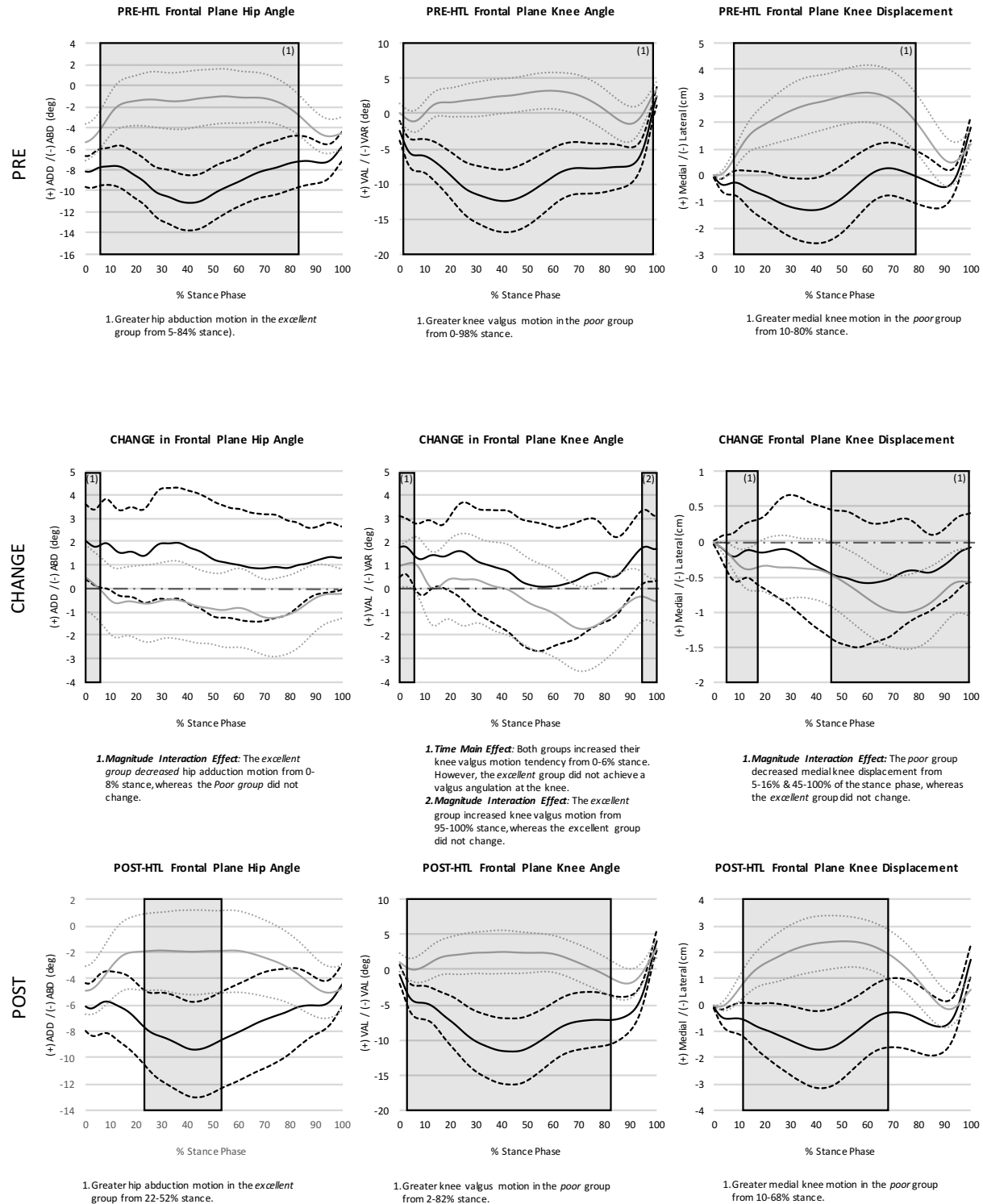


Figure 5.4 – Pre-HTL, Post-HTL, & Change Responses for Frontal Plane Hip & Knee Kinematics

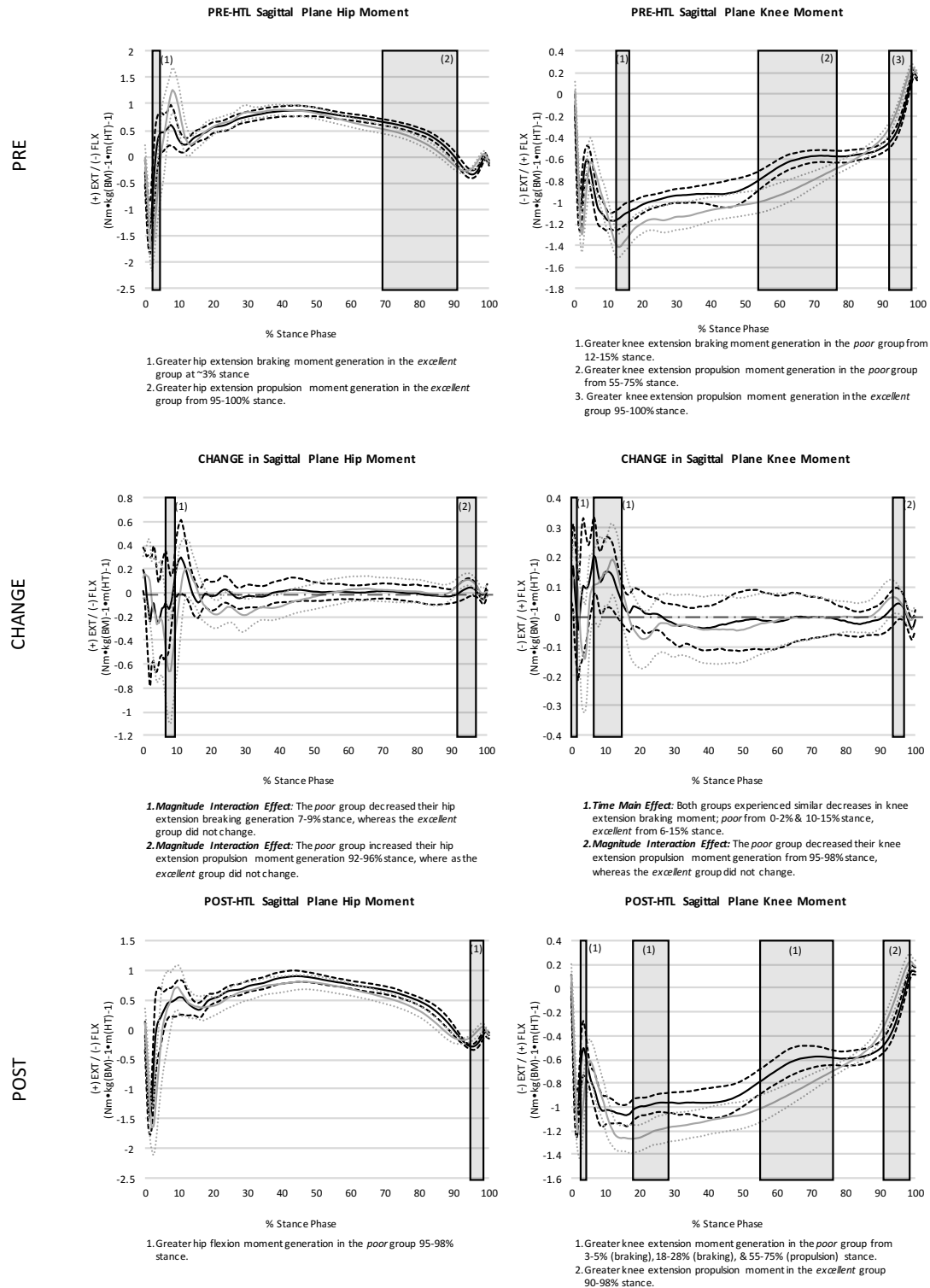


Figure 5.5 – Pre-HTL, Post-HTL, & Change Responses for Sagittal Plane Hip & Knee Moments

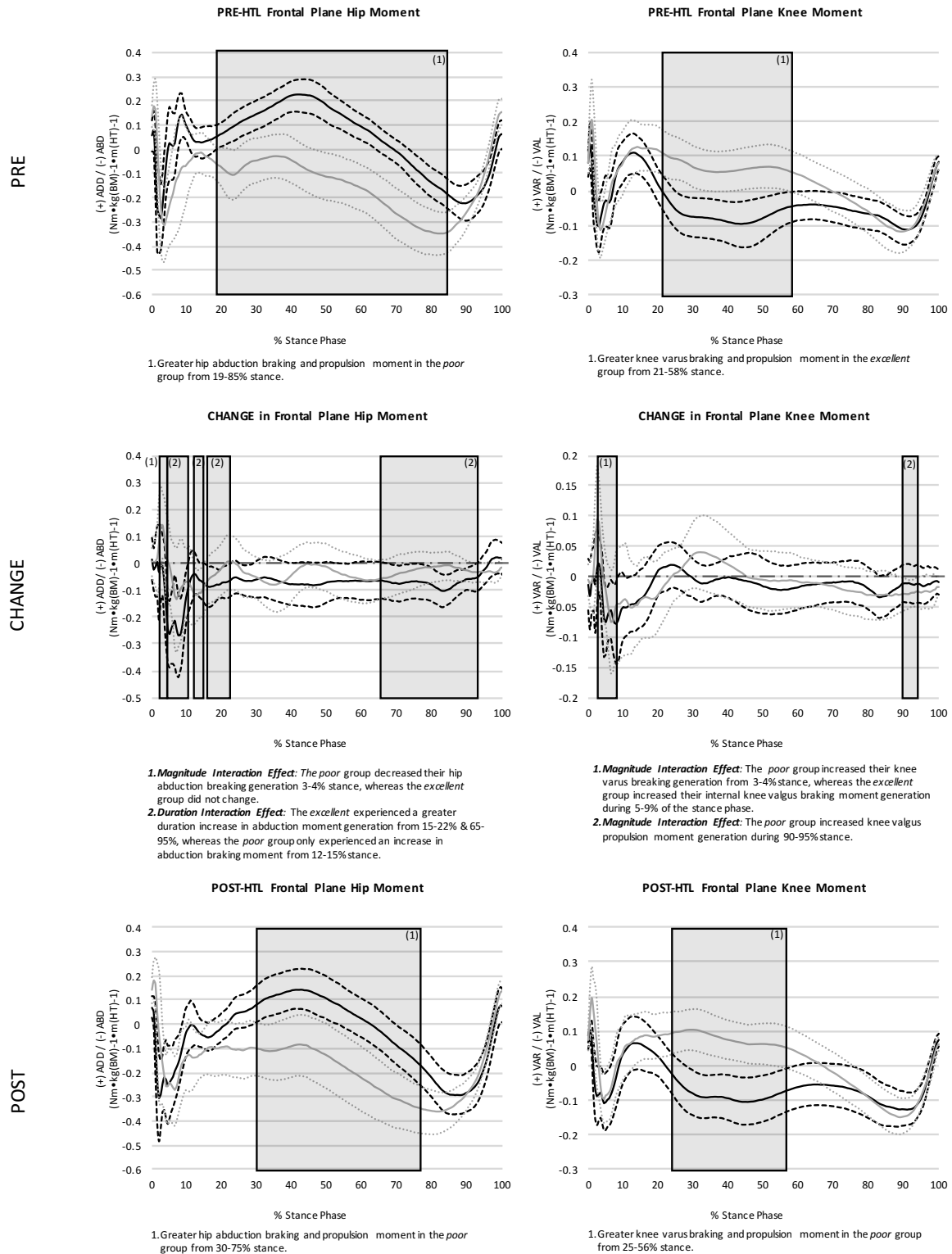


Figure 5.6 - Pre-HTL, Post-HTL, & Change Responses for Frontal Plane Hip & Knee Moments

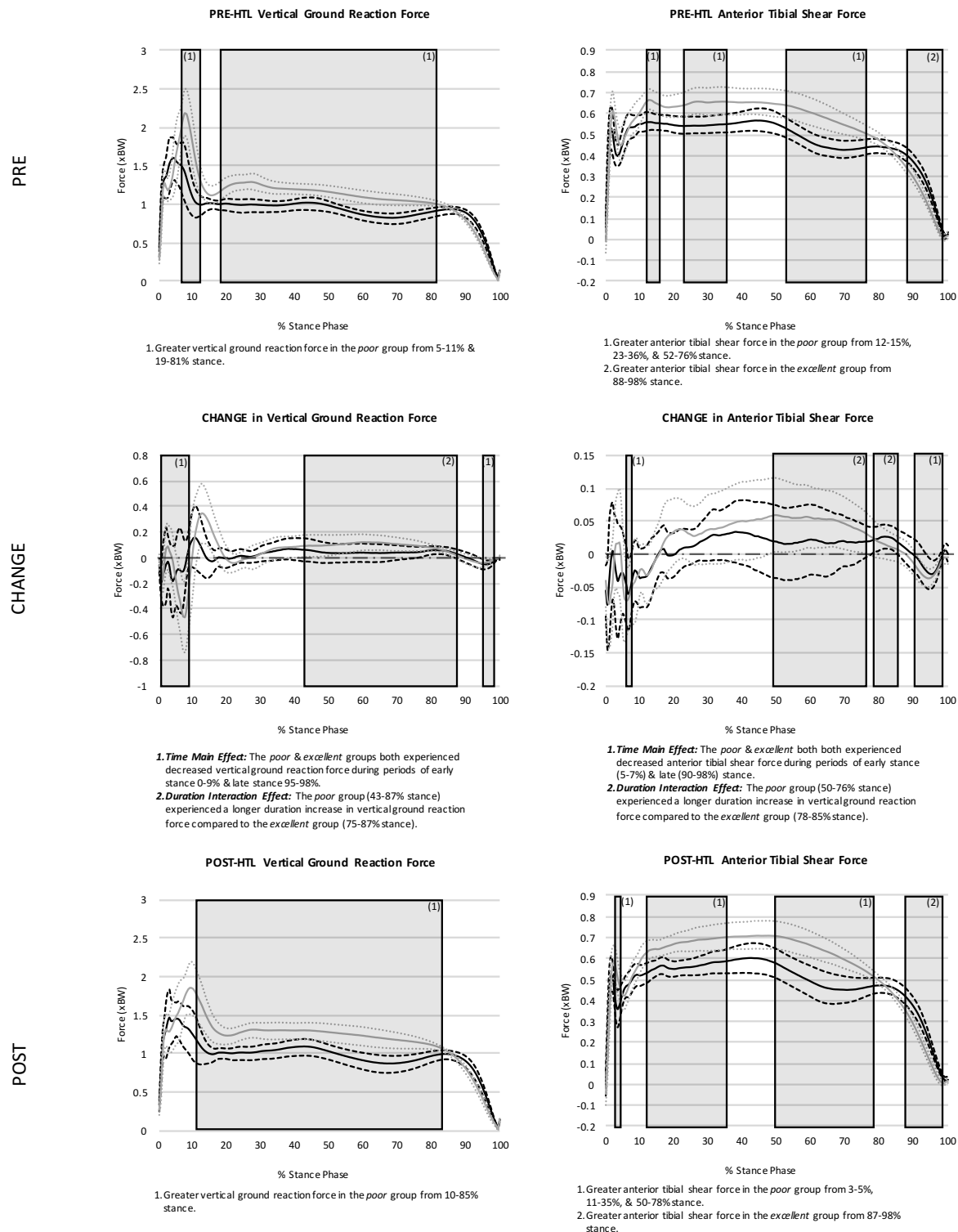


Figure 5.7 - Pre-HTL, Post-HTL, & Change Responses for Vertical Ground Reaction and Anterior Tibial Shear Forces.

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CHAPTER 6: MANUSCRIPT #2

Movement Quality Influences Systemic Stress Hormones and Musculoskeletal Tissue Responses to Acute High Training Load Exposure

Overview

Background: Recent literature has described a strong relationship between high training loads (HTL) and lower extremity musculoskeletal (MSK) injury risk in the physically active population. While a correlation exists between HTLs and lower extremity MSK injury risk, the interaction between HTL and biomechanics associated with an elevated risk or are protective against injury has not yet been described. Understanding the influence a low and high risk injury movement profile has on systemic and MSK system stress may offer insight regarding the capacity of the MSK system to offset some of the consequences of excessive HTL exposure linked to injury.

Aim: Explore the potential influence of movement profile on physiological markers of systemic and MSK tissue stress at rest and in response to an acute exposure to a controlled HTL in healthy, physically active college-aged females, a population at high risk of severe lower extremity MSK injury.

Methods: 43 physically active, healthy, college-aged females were enrolled in this study and were assigned to a *poor*-high injury risk or *excellent*-low-injury risk movement profile group operationally defined by the Landing Error Scoring System (LESS). Circulating markers of systemic (Cortisol) and MSK tissue (Creatine Kinase – MM (CK-MM) & Cartilage Oligomeric

Matrix Protein (COMP)) stress were sampled via venipuncture at rest, immediately after, and 30 minutes post HTL exposure. Samples were processed and analyzed via commercially available ELISA kits.

Results: There is a moderate to strong group effect for movement profile on resting ($d=1.19$) and post HTL ($d=0.64$) cortisol levels. Both *poor* and *excellent* groups exhibited similar relative HTL-induced response ($\% \Delta$) in cortisol, however, individuals with a *poor* movement profile exhibited elevated cortisol at baseline and post HTL compared to the *excellent* group. An *excellent* movement profile appears to encourage greater CK-MM release into circulation following HTL. Finally, there was an isolated main effect for time on COMP, with both groups experiencing similar increases in circulating COMP post HTL exposure, with similar baseline and post HTL values.

Conclusions: A *poor* movement profile is associated with elevated biomarkers of systemic stress and less release of CK-MM into circulation secondary to HTL exposure. Movement profile may moderate systemic stress levels via a high or low level of biomechanical efficiency and shielding against or amplifying mechanical loads experienced during physical activity such as those during HTL. Individuals with an *excellent* movement profile may employ a greater volume of muscle tissue to dynamically temper forces as they pass along the kinetic chain, potentially explaining the elevated levels of CK-MM observed in the more efficient *excellent* movement group.

INTRODUCTION

Recent research links high training loads to increased MSK injury rates.(Gabbett, 2004; Gabbett & Jenkins, 2011) Training load literature differentiates between internal and external loads.(Halsen 2014b) External load measures objectively define the total mechanical work completed by (or imposed demand on) an athlete during a training or competition session, such as distance traveled on a playing field, total power output, as well as number of collisions in contact sports.(Halsen 2014a; Gabbett and Ullah 2012; Colby et al. 2014) Whereas internal load is most succinctly described by Halsen et al. as “*the relative physiological and psychological stress*” experienced by an athlete in response to an external training or competition activity.(Halsen 2014b) Both external(Hulin et al. 2016; Gabbett 2015) and internal training loads(Gabbett and Jenkins 2011) are associated with MSK injury risk in the athletic population. It is important to understand those factors that influence the stress response to heavy training loads given the emerging importance of training load as a MSK injury risk factor.

There are several biochemical markers used to quantify the stress response following acute heavy training load (HTL) exposure.(Rietjens et al. 2005; Petibois et al. 2002; A. J. Coutts, Wallace, and Slattery 2007) The literature consistently describes serum cortisol to be indicative of systemic stress,(Dallman et al. 1994; Mastorakos et al. 2005) creatine kinase (CK-MM) to be representative of skeletal muscle tissue stress(Baird et al. 2012) or damage(Brancaccio, Maffulli, and Limongelli 2007), and cartilage oligomeric matrix protein (COMP) to be associated with articular cartilage disruption(Mündermann, Dyrby, Andriacchi, and King 2005; Lotz et al. 2013) during intensive exercise exposure. Thus, understanding the response of these biochemical markers to acute HTL may provide insight into the underlying mechanisms through which heavy training loads may influence MSK injury.

Individuals with specific biomechanical profiles experience greater physical stress during functional tasks, such as landing from a jump. Clinical movement assessments such as The Landing Error Scoring System (figure 6.1) have been used as a reliable and valid clinical tool to discriminate between individuals with *excellent* and *poor* movement quality profiles.(Padua et al., 2009) “Stiff” sagittal plane landing biomechanics and excessive medial knee displacement movement patterns are commonly associated with *poor* movement quality, and are linked to numerous lower extremity injuries, including ACL rupture,(Walden et al. 2015) patellofemoral pain syndrome,(Elias et al., 2004; Mizuno et al., 2001) medial collateral ligament injury,(Hull, Berns, Varma, & Patterson, 1996) lower-leg stress fracture,(Cameron, Peck, & Owens, 2014) as well as the progression of knee osteoarthritis (OA).(Brouwer et al., 2007; Sharma et al., 2001) Furthermore, a clinically identified *poor* movement profile has been associated with higher loading biomechanics, such as elevated vertical ground reaction forces, anterior tibial shear forces at the knee , and greater frontal and sagittal plane torques about the knee and hip.(D. A. Padua et al. 2009) While various individual characteristics and the training environment combine to effectively determine an athlete’s internal training load,(Impellizzeri, Rampinini, and Marcora 2005) it is possible that an interaction exists between an individual’s movement quality profile and their systemic and tissue specific response to high training loads.

Therefore the purpose of this study was to better understand the influence of movement profile on physiological markers of systemic and MSK tissue stress at rest and in response to an acute exposure to a controlled high training load (HTL) in healthy, physically active college-aged females, a population at high risk of severe lower extremity MSK injury.(Hootman, Dick, and Agel 2007; Arendt, Agel, and Dick 1999) Previous studies have identified limited sagittal plane trunk, hip, and knee motion and excessive frontal plane knee and hip motion to be

associated with a non-contact severe injury mechanism, specifically ACL rupture.(Krosshaug et al. 2007; Sheehan, Sipprell, and Boden 2012) We hypothesize individuals with inefficient *poor* high-load, “stiff” sagittal plane and uncontrolled frontal plane landing biomechanics associated with lower extremity injury (figure 6.1) will have greater resting serum COMP levels at baseline, and will experience greater elevations in cortisol and CK-MM in response to HTL. Conversely, we hypothesize that individuals with a low-load, sagittal plane dominant, *excellent* movement profile will exhibit less COMP in circulation at baseline, and experience a blunted COMP and CK-MM elevation in response to HTL.

METHODS

Participants

This study employed a two-group, cross-sectional, repeated measures design to investigate the influence of *poor* and *excellent* movement profiles on physiological markers of systemic and MSK tissue stress at rest and in response to an acute exposure to a controlled HTL (Figure 6.2).

Participants were recruited from the female student body at The University of North Carolina at Chapel Hill. A priori power analysis of previously published data revealed that a total sample size of 40 participants (*poor* (n=20) & *excellent* (n=20)) would allow the investigators to detect a minimum 20% change in biochemical markers of systemic,(A C Hackney and Viru 1999) muscle tissue,(McLellan, Lovell, and Gass 2011) and cartilage stress(Hamann et al. 2014; Niehoff et al. 2010) variables from pre- to post-HTL with a power of at least 0.80 and $\alpha = 0.05$. Participants were demographically eligible if they had a history of participating in at least the high-school varsity-level of soccer, basketball, rugby, lacrosse, and team handball, tennis, track

and field, volleyball, or field hockey. Specifically, eligible participants were 18 – 25 years of age, actively participating in at least 30 minutes of moderate to high-intensity physical activity a minimum of 3 days per week. Participants were ineligible for participation if they had no history of lower extremity surgery within the past year, lower extremity joint surgery, prior ACL or meniscal injury, lower extremity injury in the past six months that prevented participation in physical activities for more than three consecutive days, neuroendocrine, neurological, or metabolic disease or condition, or dysmenorrhea or amenorrhea within the past six months.

Demographically eligible participants were enrolled in this study if they demonstrated a operationally defined *poor* or *excellent* baseline movement profile during a LESS assessment described by Padua et al (Figure 6.2.1.).(D. A. Padua et al. 2009) Enrolled participants also needed to achieve an estimated maximal oxygen uptake ranging from 40 – 50 ml•kg⁻¹•min⁻¹ via submaximal aerobic power assessment described below. The selected aerobic power range is representative of a “good to superior” aerobic fitness level within the population (Medicine, 2009), and coincides with the representative of the college female field and court sport athlete’s aerobic power (Enemark-Miller, Seegmiller, and Rana 2009). A total of 45 participants out of 157 demographically eligible participants screened into the study, meeting all movement and aerobic power inclusion criteria. However, two participants who screened into the *poor* group could not complete the controlled HTL protocol, thus a total of 43 participants (N=43; *excellent* (n=22), *poor* (n=21)) were included in the final study sample. Participant demographics are described below in table 5.2.1.

Pretest Guidelines

Participants meeting all demographic and movement profile inclusion criteria returned to the research laboratory for their testing session within two weeks of their LESS assessment. Prior to leaving the screening session, the principal investigator (BF) verbally explained all pretest guidelines and provided the participants with a documentation packet outlining the study protocol and the pre-test guidelines for their personal reference. Additionally the packet contained a physical activity readiness questionnaire (PAR-Q), Marx activity scale, health history, menstrual cycle, and contraception usage questionnaires to be completed prior to their scheduled visit. Pretest guidelines required that all participants refrain from alcohol consumption at least 48 hours prior to the testing session, refrain from using diuretic medications or supplements 7 days prior to the testing session, avoid caffeine consumption at least 12 hours prior to their testing session, maintain their “habitual” diet at least 7 days prior to testing, maintain adequate hydration at least 24 hours prior to the testing session, and achieve at least 6 hours of sleep the night before their scheduled testing appointment.

Participant Preparation

All procedures were approved by the biomedical institutional review board (IRB) at The University of North Carolina at Chapel Hill. Enrolled participants reported to the laboratory for a single-testing session. To control for the diurnal variation of cortisol, (Kirschbaum et al. 1999) all participants reported to the research laboratory between 14:00 and 16:00 for their testing sessions. Upon arrival to the research laboratory informed consent was obtained prior to initiation of the study protocol outlined in figure 6.2. After informed consent was obtained, the

principal investigator verified the information in the pretest questionnaires to confirm the participant had no contraindications for exercise and met inclusion criteria.

Upon completion of informed consent and inclusion criteria verification procedures, participants provided a mid-stream urine sample for evaluation of their hydration level using the specific gravity technique via refractometry (TS Meter, American Optical Corp., Keene, New Hampshire, USA) to ensure adequate hydration (urine specific gravity ≤ 1.02) prior to exercise.(Stuempfle and Drury 2003) Height (cm) and mass (kg) were measured and recorded using stadiometer and a digital scale (Detecto 2381, Detecto, Webb City, Missouri, USA).

Prior to collection of the participant's baseline blood sample collection, they sat atop a treatment table in the research laboratory for exactly 30 minutes of rest. Participants were instructed to not step down from the table to ensure standardization of baseline blood samples in efforts to limit the effects of previous daily activity on cartilage, muscle and stress biomarkers at baseline.(Niehoff et al. 2011)

Ventilatory Threshold Assessment

For determination of ventilatory threshold, participants completed a speed-only graded submaximal aerobic capacity assessment(Vanhoy 2012; Berry et al. 2016) on a motorized treadmill (GE T2100 Exercise Stress System General Electric) with measurement of respiratory gas exchange using a metabolic cart (TrueOne 2400 Metabolic Measurement System Parvo Medics) and instantaneous monitoring of heart rate (A39 Exercise Monitor Under Armour Inc.). Prior to the ventilatory threshold assessment, the principal investigator completed standard calibration procedures of the flow, carbon dioxide, and oxygen sensors of the metabolic cart using a 3.0 L syringe of known gases. The principal investigator described the ventilatory

threshold assessment protocol to the participant before the initiation of the evaluation procedures (figure 6.2).

After the principal investigator delivered testing instructions and explained the assessment procedures, the participant's resting heart rate, blood pressure (ADC 700 Diagnostix® Series Pocket Aneroid Sphygmomanometer American Diagnostics Corporation; 3MTMLittmann® Stethoscope 3M), were measured and recorded after sitting for five minutes. The principal investigator then reviewed the participant's resting vital signs to ensure there was no evidence of contraindications to participation in submaximal exercise.(Medicine, 2009)

After the principal investigator ensured there were no contraindications to exercise participation, the ventilatory threshold assessment protocol outlined in figure 6.2 was initiated. Following completion of the ventilatory threshold assessment, the participant's ventilatory threshold was determined using a modified V-slope method (Sue et al. 1988) to identify when there was an observed increase in ventilatory equivalent for oxygen without an accompanying increase in the ventilatory equivalent for carbon dioxide(Davis, Whipp, and Wasserman 1980) in the participant's respiratory gas exchange data sampled during the assessment protocol. The VO_2 and treadmill speed coincident with 100%, 110%, and 120% were identified, and used to define the control of the treadmill running speed during the HIEE protocol (figure 6.2)

Controlled Acute High Training Load Exposure Protocol

The controlled HTL protocol deployed in this study was novel (figure 6.2). Previously described HTL protocols lack rigorous control of intensity to compare the dependent variables of interest in the current study between movement profile groups. Thus the internal load(Foster et al. 2001) the study participants experience may be variable based on fitness level and other

confounding individual physiological variables.(Foster et al. 2001) The stringent aim of this study's HTL protocol was to expose participants to approximately identical internal training loads based on their individualized ventilatory threshold.

Controlling the HTL intensity using this novel approach implied individuals should have used similar energy systems,(Hopker, Jobson, and Pandit 2011) and experienced the same relative exercise intensity based on their individual system physiology.(Davis, Whipp, and Wasserman 1980; Hopker, Jobson, and Pandit 2011) During the HTL, the treadmill speed was increased or decreased by $0.161 \text{ km}\cdot\text{h}^{-1}$ increments to maintain an individualized instantaneous VO_2 coincident with 100 – 120% ventilatory threshold, RER between 0.85 – 0.95, and RPE 12 – 15. At end of each minute of each stage (5 stages, 5 minutes) of the HTL protocol, treadmill speed, RPE, VO_2 , and RER were manually recorded and entered into a Microsoft Excel spreadsheet (Microsoft Excel Microsoft Corporation). The stringent control of relative exercise intensity across subjects and between groups permitted isolated identification of the effects of an individual's movement profile on their physiological markers of systemic and MSK tissue stress in response to a nearly identical exercise intensity exposure.(Hopker, Jobson, and Pandit 2011)

Blood Collection Procedures

Following the standardized 30 minute rest period, all participants had their blood drawn from their antecubital vein using a 20 G $1\frac{1}{2}$ BD PrecisionGlideTM vacutainer needle in a seated position. The blood sample was collected into a single 10 ml serum separator tube with clot activator gel (BD SST Vacutainer). The 10 ml blood sample was stored at 2 – 4°C and allowed to clot overnight prior to processing and long-term storage. Blood was collected at three separate time points during the study protocol; PRE as described above, immediately following the HTL

exercise bout (POST-0), and 30 minutes after the HTL bout (POST-30). After samples clotted overnight, they were transferred to a pre-cooled centrifuge (IECCentra-8R Refrigerated Centrifuge) and were spun at 3,000 RPM for 15 minutes at 4° C. Serum was collected from the tubes via a 2.0 ml transfer a pipette into four aliquots for each time point (12 aliquots) into sterile 2.0 ml polypropylene long-term storage cryogenic vials (Nalgene Thermo Scientific). Vials were labeled, sealed, and stored at -80° C until thawing for serum biomarker analysis via ELISA procedures described below.

Biochemical Analysis

The selected systemic stress, cartilage, and muscle tissue stress biomarkers were analyzed using commercially available ELISA kits (abcam cortisol, Abnova COMP, MyBioSource CK-MM). All biomarkers were assessed at PRE for a baseline value. The post HTL values for Cortisol and CK-MM were assessed at POST-30,(A C Hackney and Viru 1999; Brancaccio, Maffulli, and Limongelli 2007) while the post HTL values for COMP were assessed at POST-0.(Niehoff et al. 2010) The results of the biomarker assays were assessed in duplicate using a 96 well, 8-channel microplate reader (ChroMate[®] 4300, Awareness Technology Inc., Hauppauge, New York, USA). Cortisol was read at 450 nm, COMP at 405 nm, and CK-MM at 450 nm per manufacture guidelines. All samples from an individual participant were analyzed on a single ELISA plate. The intra-assay coefficients of variation for cortisol, COMP, and CK-MM were 1.57%, 5.88%, and 7.14% respectively. The inter-assay coefficients of variation for cortisol, COMP, and CK-MM were 4.48%, 3.20% and 11.1% respectively.

Statistical Analysis

All results were analyzed using SPSS statistics (Version 21 IBM). Descriptive statistics for biomarker, participant anthropometric data, and metabolic data collected during the HTL were calculated. The level of significance for all hypothesis tests was set at $\alpha < 0.05$ *a priori*. Independent samples *t*-tests were carried out to determine if there was a difference in anthropometrics and fitness levels between movement profile groups. A 2×5 mixed model analysis of variance (ANOVA) was carried out to determine if there was an effect of movement profile on metabolic data across the stages of the HTL.

Due to the inherent variability in raw biomarker data, all raw serum concentrations were natural log transformed to establish normality for statistical analyses using a 2×2 mixed model ANOVA to evaluate the effects of group and time on biomarker concentrations pre and post HTL. *Post hoc* analyses using group-by-time means and 95% confidence intervals were used to evaluate multiple comparisons. The lack of overlap between 95% confidence intervals around group-by-time means was used for criterion for statistical significance. (Poole 2001; Dijkers 2013) Additionally, independent samples *t*-tests were carried out to compare $\Delta\%$ scores for raw biomarker data to further evaluate the presence of a significant difference in a biomarkers response to HLT between groups. (G. Fitzmaurice 2001; G. M. Fitzmaurice, Laird, and Ware 2011) The log concentrations of biomarkers were backwards log transformed for data presentation and interpretation within the context of previous literature.

Although systemic and tissue stress biomarker levels were assessed for all participants, in some samples, individuals presented with levels outside a physiological range, did not have viable pairs of pre and post HTL secondary to compromised sample integrity, or presented as statistical outliers >2 standard deviations outside the log-transformed group-by-time sample

means. To control for missing data, a list-wise deletion was applied such that the final number of participants with valid pre and post HTL values for cortisol was (*excellent* (n=19), *poor* (n=21)), COMP was (*excellent* (n=21), *poor* (n=20)), CK-MM (*excellent* (n=21), *poor* (n=18)). Finally, chi-square analyses of association were carried out to determine if there was an relationship between movement profile group with “responders” who increased their levels of circulating biomarkers or “non-responders” who maintained or decreased their levels of circulating biomarkers of interest.

RESULTS

Participants Demographics

Participant anthropometrics and fitness demographic data are presented in table 5.2.1. Independent samples *t*-tests revealed there was no significant ($P>0.05$) differences between the movement groups for any demographic or fitness variable.

Controlled High-Intensity Exercise Exposure Metabolics & Perceived Intensity

Movement profile group means, standard deviations, and 95% confidence intervals are reported in table 5.2.2. The results of the 2×5 mixed model ANOVA analyses revealed there was no significant ($P>0.05$) group-by-time (exercise stage) interaction or any group main effects. There was a significant main effect of exercise stage for RER, RPE, heart rate and VO_2 ; with a significant increase between stage #1 and all other stages in both groups ($P<0.05$) primarily driven by the difference in initial metabolic activity in response to exercise onset (Brooks 1985) between stage #1 and the remaining stages.

Circulating Systemic & Musculoskeletal Tissue Stress Biomarkers

Group mean % Δ , baseline and post HTL raw unit (ng/ml) and natural log transformed concentration values of systemic and musculoskeletal tissue stress biomarkers for the *poor* and *excellent* groups are presented in table 5.2.3 along with the associated group-by-time standard deviations, 95% confidence intervals, and effect size calculations between movement profiles at each time point. Sample means and descriptive statistics collapsed across movement profile groups for the main effect of time are reported in table 5.2.4. Mixed-model ANOVA analyses did not identify a significant group-by-time interaction effect for any of the biomarkers ($P > 0.05$). However, upon closer analysis of the group-by-time CK-MM means and their associated 95% confidence intervals, it appears there is substantial separation between the *poor* group's upper, and the *excellent* group's lower bounds for both the the log-transformed and raw post HTL concentration values, with a moderate-to-large effect size. Furthermore, the *excellent* group exhibited a significantly greater % Δ for CK-MM ($P < 0.05$) compared to the *poor* group, thus implicating a greater average within-subject CK-MM elevation in response to the HTL in the *excellent* group, that may not be accounted for with the general linear model ANOVA. (Dijkers 2013; G. M. Fitzmaurice, Laird, and Ware 2011)

In addition to a greater CK-MM elevation in response to acute HTL, there was a significant main effect for group on CK-MM, with the *excellent* group having greater overall CK-MM relative to the *poor* group ($P < 0.05$). There was a significant main effect for time on COMP resulting in higher levels post HTL ($P < 0.05$). Additionally, there were significant main effects for group ($P < 0.05$) and time ($P < 0.05$) on cortisol. Interestingly, while the *poor* and *excellent* group's respective pre and post HTL cortisol values and associated 95% confidence intervals remained separated at each time point. There was substantial overlap in the *poor*

group's pre HTL and *excellent* group's post HTL cortisol 95% confidence intervals. Within the context of the the main effects for group and time on cortisol, these results recognize the *poor* group to have exhibited a resting cortisol level that is similar to the *excellent* group's post HTL cortisol levels. Furthermore, there were no significant associations between movement quality profile and responder-type for any of the biomarkers ($P>0.05$).

DISCUSSION

The most important findings of this study are that there is a large effect of an individual's movement quality profile on circulating biochemical markers before and after an acute HTL. Specifically we observed a strong effect of movement quality profile on CK-MM response to an acute HTL, with greater CK-MM increase in the *excellent* movement profile group. Additionally, circulating systemic stress hormone levels (cortisol) at rest and following acute HTL were higher in the poor movement profile group. In summary our findings suggest that CK-MM is released in larger amounts following acute HTL in those with an excellent movement profile. Also, those with a poor movement profile are consistently exposed to greater levels of circulating cortisol compared to their *excellent* movement profile counterparts. These findings indicate that movement quality profile influences markers of systemic (cortisol) and muscle (CK-MM) stress.

To our knowledge this is the first study to investigate the effects of movement quality on training load biomarkers associated with a systemic (cortisol) and tissue (CK-MM & COMP) stress response to acute HTL. Our systemic stress and CK-MM findings are in agreement with previous studies that have reported acute HTL to induce similar increases in cortisol(Edwards and Kurlander 2010; Edwards and Casto 2013; Haneishi et al. 2007; Aizawa et al. 2006) and CK-MM(Sougliis et al. 2015; Keane et al. 2015) in female field or court sport athletes. The

results of the current study implicate biomechanics have a strong effect on basal systemic stress levels and muscle tissue stress responses to acute HTL, but no apparent influence on cartilage stress as we observed no group differences in COMP measures before or after acute HTL.

Cortisol

Cortisol is a downstream indicator of hypothalamic-pituitary-adrenal axis activity to maintain homeostasis in response to stress (Selye 1952; Dallman et al. 1994) both at rest and during exercise.(Mastorakos et al. 2005; Anthony C Hackney 2006; Steinacker et al. 2004; Dallman et al. 1994) Thus, interpreting the current findings within the context of integrated systemic physiology,(Brooks 1985) it is evident *poor* movement quality results in elevated stress levels at rest and following exercise. It is without question that there are many possible explanations and theories that must be explored as a consequence of the current study's results. However, within the framework of the current investigation two viable explanations underlying the observed findings arise; (1) Poor movement quality results in greater energy demand, thus greater need for substrate mobilization both at rest and during exercise. (2) Poor movement quality results in higher mechanical stress exposure, which results in an elevated systemic inflammatory response.

It is thus possible that exposure to the same internal and external load (Table 5.2.2.) resulted in a greater need for substrate mobilization in the *poor* group compared to that of the *excellent* group, suggestive of a “mechanochemically inefficient”(Ryschon et al. 1997; Baird et al. 2012) system. One of the global aims of the downstream release of cortisol subsequent to exercise-induced elevations in hypothalamic-pituitary-adrenal axis activity is to elicit the sympathetically driven “fight or flight” response with an effective capacity to rapidly mobilize

various energy stores in effort to provide energy substrates to active muscle tissue and maintain blood glucose levels and systemic homeostasis.(Dallman et al. 1994; Mastorakos et al. 2005).

The *poor* movement quality profile is associated with inefficient energy absorption and production.(Norcross et al. 2013a; Norcross et al. 2013b; D. A. Padua et al. 2009; D. a. Padua and DiStefano 2009) Increased cortisol in the poor movement profile group at rest ($d=1.19$) and after exposure to acute HTL ($d=0.64$) implicates their movement profile may result in an elevated chronic need to mobilize of energy stores in effort to meet the metabolically inefficient demands of the their biomechanical profile.

While we did not measure biomarkers of systemic inflammation such as the inflammatory cytokines(Nielsen and Pedersen 2007; Steinacker et al. 2004) to lend support to our chronic inflammatory theory, it is well-established that cortisol is a potent endogenous anti-inflammatory substance capable of combating the consequences of exposure to oxidative stress molecules that are a consequence of acute HTL and sport.(Mastorakos et al. 2005; Dallman et al. 1994; Steinacker et al. 2004)(A. Coutts et al. 2007)(McLean et al. 2010) Secondary to HTL an elevation in cortisol is expected, and is considered a normal physiological response to exercise. However, elevations at rest are representative of potentially non-physiological system responses to a stressor.(Anthony C Hackney and Battaglini 2007; Meeusen et al. 2013) The higher cortisol values observed in the *poor* group relative to the *excellent* group are not within the pathological range of hypercortisolism or baselow's type over-training / reaching syndromes.(Dallman et al. 1994; Petibois et al. 2002; Carfagno and Hendrix 2014) However, the elevation in the *poor* group's circulating cortisol at baseline may suggest a greater basal systemic stress level in the *poor* movement profile group.

The exact etiology of this elevated stress level cannot be determined from this study. However, over-training / over-reaching literature may offer an explanation. Over-training syndrome in its simplest form is described as a pathology resulting from cumulative imposed stress outside the recovery capacity of the athlete, eventually resulting in a set of symptoms and maladaptation associated with decreased performance that does not return within a few days of rest / recovery.(Anthony C. Hackney, Pearman, and Nowacki 1990; Anthony C Hackney and Battaglini 2007; Halson and Jeukendrup 2004) We do not propose the *poor* movement group participants to be suffering from over-training. Rather we are choosing to leverage a similar model of over-exposure to mechanical stresses associated with a *poor* movement profile to elicit greater induced basal hypothalamic-pituitary-adrenal axis activity in this subgroup of the population that requires further study. It is possible the *poor* group is consistently in a state of a sub-pathological inflammatory / recovery response secondary to exposure to an elevated mechanical load during their activities of daily life and athletic participation compared to the *excellent* group. Collectively, our findings suggest that physically active females with a *poor* movement profile are consistently exposed to greater amounts of circulating cortisol compared to their *excellent* movement profile counterparts.

Creatine Kinase (CK-MM)

The *excellent* movement quality profile group exhibited a greater increase in CK-MM compared to the *poor* group following acute HTL. We believe that elevated CK-MM in the *excellent* movement profile group represents greater skeletal muscle tissue usage during the acute HTL protocol, which is an efficient and preferred mechanism rather than relying on passive soft tissue structures. Based on our inclusion criteria for the *excellent* movement profile group, these

individuals displayed greater sagittal plane displacement of the hip and knee during the landing tasks.(D. A. Padua et al. 2009; D. a. Padua and DiStefano 2009) Increased hip and knee flexion displacement suggest greater eccentric lengthening of the large hip extensor (gluteus maximus and hamstrings) and knee extensor (quadriceps) musculature during landing in the *excellent* movement profile group.

There is a large body of evidence identifying eccentric muscle contraction to result in the greatest release of CK-MM into circulation.(Clarkson and Hubal 2002; Ryschon et al. 1997; Saka et al. 2009; Chen and Hsieh 2001) Thus it is likely the *excellent* group's movement strategy (greater hip and knee sagittal plane displacement) during the HTL resulted in a greater volume of eccentric lengthening of the hip and knee extensor musculature, prolonging the dissipation of force over a greater period of time, and thus permitting attenuation of ground forces within a greater volume of muscle tissue which has been observed to increase circulating CK-MM.(Barroso et al. 2010; Baird et al. 2012) The *excellent* group's landing strategy may result in a more "mechanochemically efficient" strategy to conserve energy by leveraging the efficiency of the eccentric contractile properties of muscle over the stretch-shortening cycle.(Comyns, Harrison, and Hennessy 2011; Horita et al. 1999; Ryschon et al. 1997)

Originally, the creatine kinase enzyme was associated with muscle tissue damage secondary to myocardial infarction, implicating an elevation in serum creatine to be suggestive of a purely catabolic and potentially pathological state.(Baird et al. 2012) However, previous literature that has evaluated the integrated physiological role and implications of the CK-MM creatine kinase isoenzyme during exercise lends support to our findings.(Baird et al. 2012; Saks 2008) Recent theory and understanding of the CK-MM isoenzyme, which was specifically analyzed in this study, posits an emerging theory.(Lo et al. 2010; Baird et al. 2012) Specifically,

elevated CK-MM serum concentration secondary to acute HTL suggests an elevation in serum CK-MM to represent normal muscle activity during exercise, and is a healthy physiological response.(Baird et al. 2012; Ryschon et al. 1997; Saks 2008) Contemporary investigations support the theory that elevated serum CK-MM may be a marker of greater utilization of skeletal muscle to eccentrically control motion in the *excellent* movement quality profile group, representative of a physiological response to exercise within this population.(Baird et al. 2012; Saks 2008)

The “mechanochemical inefficiency” of the *poor* movement profile is further supported by our CK-MM findings, suggesting the *excellent* movement profile group may have leveraged a more efficient strategy to absorb and generate force during the HTL. Interestingly, high-velocity eccentric and concentric muscle contractions over a restricted range of motion have been observed to result in *greater* energy demand(Baird et al. 2012; Newham, Jones, and Clarkson 1987; Clarkson and Hubal 2002) yet *lower* CK-MM release into circulation.(Barroso et al. 2010) The *poor* group used a “stiff” landing strategy, requiring a high-force, high-velocity eccentric contraction over a shorter joint range of motion at the knee, hip, and trunk. Suggesting that the *poor* movement group may use a movement strategy that is both metabolically inefficient at the muscle tissue level and releases less CK-MM into circulation under exercise conditions secondary to a “stiff” movement profile limiting eccentric muscle activity.

The last explanation of elevated CK-MM in the *excellent* group is afforded by the widely accepted role of adenosine monophosphate-activated protein kinase (AMPK) as an “energy sensing enzyme”(Baird et al. 2012; Brooks 1985) that may play a role in the offloading of CK-MM from the eccentrically active muscle tissue in the *excellent* group. The primary bioenergetic roll of creatine kinase is to maintain phosphocreatine levels in the cell to be readily

available for immediate energy release.(Brooks 1985) However, during sustained exercise, as in our HTL protocol CK-MM's roll is superfluous, and AMPK's actions to turn off non-essential ATP consumption may act in attempt to override the utilization of CK-MM to resynthesize creatine-phostphate, by expelling CK-MM from the cytosol to make energy substrates readily available for more efficient oxidative pathways instead.(Saks 2008) Furthermore, offloaded CK-MM reduces the availability of energy substrate for rapid muscular contraction post-exercise often reported as a decrease in muscle power output with higher levels of CK-MM in circulation.(McLellan, Lovell, and Gass 2011; A. Coutts et al. 2007; Magal et al. 2010) The lack of CK-MM within the cytoplasm may act as a protective mechanism permitting appropriate recovery of muscle for subsequent bouts of physical activity, protecting itself from high-power force output contractions.(Baird et al. 2012)

When interpreting our CK-MM and cortisol results together, our findings are in agreement with the position of Baird et al. 2012 that higher levels of circulating CK-MM may not be directly indicative of dangerous skeletal muscle damage alone. The *excellent* movement profile group did not exhibit a cortisol response associated with pathology which would be expected in parallel with a higher level of potentially injurious muscle tissue disruption. On the contrary, we observed less serum cortisol in the *excellent* group post HTL compared to the *poor* group in support of both our (1) metabolic and (2) mechanical stress theories. The current study's findings offer support for the theory that the elevated serum cortisol in the *poor* group may be a response to elevated biomechanically self-induced systemic stress exposure not attenuated by muscle tissue during physical activity.

Cartilage Oligomeric Matrix Protein (COMP)

In contrast to our original hypothesis, COMP measures did not significantly differ between groups, nor was there a difference in COMP changes following acute HTL between groups. However, we did observe a significant change in COMP following acute HTL exposure in both groups. Specifically, there was an increase in COMP ($\Delta=15.22\%$ [3.64,26.82]) following acute HTL, which did not differ between the *excellent* and *poor* movement profile groups. Previous studies have focused on primarily adult or elderly male populations. Thus, our study is the first to report the effect of a controlled acute HTL on circulating COMP in a large sample from the physically active college-aged female population. The results of this study suggest that physically active college-aged females exhibit a highly variable, yet similar COMP increase compared to previous reports in males following acute HTL.(Niehoff et al. 2010; Hamann et al. 2014; Kersting et al. 2005; Mündermann, Dyrby, Andriacchi, King, et al. 2005)

We observed a substantially greater amount of variability in resting, post HTL, and overall COMP response in the *poor* group. Suggesting, there may be a need for more advanced statistical procedures in evaluating COMP responses in the physically active healthy population, such hierarchical linear models using random intercepts and slopes.(Dijkers 2013) Closer inspection of the COMP response to acute HTL revealed there was a subset of individuals who were “non-responders” and decreased their COMP levels post-exercise. When including these individuals into the study sample’s mean $\%\Delta$ for COMP (15.22 [3.64,26.81]%), our $\%\Delta$ results are a $\frac{1}{2}$ to $\frac{1}{3}^{\text{rd}}$ less than that of previous reports with ranges from 25 – 40%+ increases overall.(Niehoff et al. 2010; Mündermann, Dyrby, Andriacchi, King, et al. 2005; Hamann et al. 2014) However, when isolating our analyses to “responders” (those who experienced some increase in COMP after acute HTL), the average response of a $\sim 37\%$ increase is aligned with the

previous literature. Overall, our findings extend the current body of training load literature by indicating that movement quality does not appear to influence the immediate COMP response to acute HTL in physically active college-aged females. However, it should be noted that COMP responses to acute HTL were highly variable, which suggests this future investigation of this measure may require a more advanced investigation. In addition, the magnitude of COMP increase following acute HTL appears similar to previous reports in males, thus there does not appear to be a sex difference in COMP response to acute HTL.

Our study is not without limitations. Lacking a measure of inflammation and blood glucose or other circulating energy substrates such as lipoproteins limits our understanding of the *poor* group's baseline elevation in cortisol. However the high-level of control of our exercise protocol (table – 5.2.2) is supported by a similar cortisol response (% Δ) between groups, lending to the notion that while movement profile does not directly affect the stress response to HTL, it may influence the resting activity of the hypothalamic-adrenal-pituitary-axis. Future investigations should implement intervention designs aimed at improving movement quality in individuals with *poor* movement profiles to determine if there is a cause-and-effect relationship between movement quality and resting cortisol levels.

The results of the current study lack generalization to other demographics within the physically active population. Our results are limited to describing the training load response profiles of healthy physically active college-aged females with a history of participation in field or court sports. While our results are not generalizable to the larger athlete and physically active population, college-aged female field and court sport athletes represent a population at high risk of non-contact, severe lower extremity injury such as ACL rupture.(Hootman, Dick, and Agel 2007; Waldén et al. 2011; Peck et al. 2013) Additionally, evaluation of COMP in this population

is novel, and offers greater insight to an expanded population's potential articular cartilage stress response to HTL previously unknown in the literature. Our observation of a high level of variability in COMP levels in this population suggests additional research of COMP responses to exercise is warranted.

In conclusion, the results of the current study suggest clinicians should consider promoting an *excellent* movement profile to limit potentially maladaptive elevations in cortisol in physically active female athletes. Promotion of an *excellent* movement profile may result in increased systemic efficiency during acute HTL exposures. The collective results of this study also implicate that the prudent clinician should take caution when independently interpreting CK-MM as a marker of tissue damage, as it may not be a fundamental marker of injurious skeletal muscle damage, and may more accurately reflect a mechanochemically efficient loading strategy. Greater movement quality appears to be associated with greater loading of dynamic muscle tissue during sport participation, which may result in less overall systemic stress exposure, promoting faster recovery from and resilience to HTL exposure.

Table 6.1 - Group Demographic & Fitness Level Descriptive Statistics; Group Means (SDs)

	Excellent (n=22)	Poor (n=21)
Age (years)	20.5 (1.9)	20.4 (1.3)
Height (m)	1.44 (0.44)	1.63 (0.23)
Mass (kg)	64.5 (7.8)	60.9 (6.1)
Resting Heart Rate (bpm)	65.0 (9.8)	71.5 (14.5)
Resting Diastolic Blood Pressure (mmHg)	73.7 (9.6)	74.3 (14.2)
Resting Systolic Blood Pressure (mmHg)	112.9 (6.4)	115.2 (7.4)
100% Ventilatory Threshold ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	33.2 (4.2)	34.0 (4.1)
110% Ventilatory Threshold ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	36.5 (4.6)	37.3 (4.5)
120% Ventilatory Threshold ($\text{ml} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	39.8 (5.0)	40.7 (4.9)

Table 6.1 – Group Demographic Descriptive Statistics

Table 6.2 Controlled Acute High Training Load Exercise Exposure Stage Metabolic & Intensity Perception Data

Mean (SD) [95% CI]	Stage 1		Stage 2		Stage 3		Stage 4		Stage 5	
	Excellent	Poor	Excellent	Poor	Excellent	Poor	Excellent	Poor	Excellent	Poor
Treadmill Speed (km•h ⁻¹)	11.0 (1.1) [10.6, 11.5]	11.4 (1.0) [10.9, 11.9]	11.0 (1.2) [10.5, 11.6]	11.3 (1.0) [10.8, 11.8]	11.0 (1.2) [10.5, 11.5]	11.3 (1.0) [10.8, 11.7]	11.1 (1.2) [10.6, 11.6]	11.3 (1.1) [10.8, 11.8]	11.2 (1.1) [10.7, 11.7]	11.3 (1.1) [10.8, 11.8]
Rate of Perceived Exertion (Borg 6-20)	12.1 (0.6) [11.5, 12.6]	11.7 (1.7) [11.3, 12.5]	12.4 (1.0) [11.8, 12.9]	12.8 (1.6) [12.2, 13.4]	12.7 (0.9) [12.1, 13.2]	13.2 (1.5) [12.6, 13.7]	13.1 (1.1) [12.5, 13.8]	13.8 (1.6) [13.2, 14.2]	13.3 (1.2) [12.7, 13.9]	13.9 (1.4) [13.3, 14.5]
Heart Rate (bpm)	169.0 (12.9) [161.9, 176.8]	170.2 (19.6) [162.9, 177.4]	175.0 (15.1) [169.1, 180.8]	180.8 (11.8) [174.8, 186.8]	177.5 (14.0) [172.3, 182.7]	182.9 (9.6) [177.6, 188.2]	179.4 (14.6) [174.2, 184.7]	183.4 (9.2) [178.0, 188.8]	181.8 (11.7) [176.2, 187.4]	180.8 (14.2) [175.0, 186.5]
Oxygen Uptake (ml•kg ⁻¹ •min ⁻¹)	35.9 (3.2) [34.4, 37.5]	35.9 (3.9) [34.4, 37.6]	36.4 (4.4) [34.7, 38.3]	37.0 (4.1) [35.1, 38.9]	37.1 (3.8) [35.5, 38.6]	37.0 (3.4) [35.4, 38.6]	37.7 (4.0) [36.0, 39.5]	38.0 (3.9) [36.2, 39.7]	38.1 (3.6) [36.5, 39.6]	37.8 (3.6) [36.2, 39.4]
Respiratory Exchange Ratio (RER)	0.83 (0.03) [0.81, 0.84]	0.83 (0.04) [0.82, 0.85]	0.88 (0.04) [0.87, 0.90]	0.89 (0.03) [0.87, 0.90]	0.88 (0.04) [0.87, 0.89]	0.88 (0.03) [0.87, 0.90]	0.87 (0.03) [0.86, 0.90]	0.88 (0.03) [0.86, 0.89]	0.88 (0.04) [0.86, 0.89]	0.88 (0.03) [0.87, 0.90]

Table 6.2 – Controlled Acute High Training Load Exercise Exposure Stage Metabolic & Intensity Perception Data

Table 6.3 - Group-by-time Raw (ng/ml), Natural Logarithm-transformed, & %Δ serum biomarker concentrations pre and post acute HTL.

	Excellent			Poor			Cohen's D
	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI	
CORTISOL ^{b,c}							
Pre Log [C]	19	4.5 (0.31)	[4.37, 4.64]	21	4.98 (0.41)	[4.8, 5.16]	1.32
Post Log [C]*	19	4.8 (0.72)	[4.48, 5.12]	21	5.33 (0.72)	[5.02, 5.64]	0.74
Pre Raw [C] (ng/ml)	19	96.62 (30.49)	[82.91, 110.32]	21	157.64 (65.49)	[129.63, 185.66]	1.19
Post Raw [C] (ng/ml)*	19	161.22 (144.55)	[96.23, 226.22]	21	252.52 (140.26)	[192.53, 312.51]	0.64
%Δ Raw [C]	19	59.99 (120.35)	[5.87, 114.11]	21	68.4 (91.22)	[29.39, 107.42]	0.08
CK-MM ^{b,d}							
Pre Log [C]	21	2.28 (0.87)	[1.91, 2.66]	18	1.97 (0.17)	[1.89, 2.05]	0.50
Post Log [C]*	21	2.58 (0.9)	[2.19, 2.96]	18	2.02 (0.24)	[1.91, 2.13]	0.85
Pre Raw [C] (ng/ml)	21	14.88 (16.99)	[7.62, 22.15]	18	7.26 (1.33)	[6.64, 7.87]	0.63
Post Raw [C] (ng/ml)*	21	20.14 (23.26)	[10.19, 30.09]	18	7.73 (2.01)	[6.81, 8.66]	0.75
%Δ Raw [C]	21	68.62 (115.61)	[19.18, 118.07]	18	7.12 (22.4)	[-3.23, 17.47]	0.74
COMP ^e							
Pre Log [C]	21	6.08 (0.26)	[5.97, 6.19]	20	6.05 (0.4)	[5.88, 6.23]	0.09
Post Log [C]**	21	6.17 (0.33)	[6.03, 6.31]	20	6.17 (0.39)	[5.99, 6.34]	0.01
Pre Raw [C] (ng/ml)	21	453.15 (121.01)	[401.4, 504.91]	20	461.12 (195.11)	[375.61, 546.63]	0.05
Post Raw [C] (ng/ml)**	21	502.5 (162.48)	[433.01, 572]	20	512.03 (201.85)	[423.57, 600.49]	0.05
%Δ Raw [C]	21	12.15 (27.83)	[0.24, 24.05]	20	18.45 (44.73)	[-1.15, 38.06]	0.17

^asignificant for group × time interaction^bsignificant for group^csignificant for time^dsignificant change score difference

*POST-30 sample

**POST-0 sample

Table 6.3 - Group-by-time Raw (ng/ml), Natural Logarithm-transformed, & %Δ serum biomarker concentrations pre and post-acute HTL

Table 6.4 - Raw (ng/ml), Natural Logarithm-Transformed, & %Δ for serum biomarker concentrations collapsed across groups pre and post acute HTL.

	Pre			Post				
	n	Mean (SD)	95% CI	n	Mean (SD)	95% CI	Cohen's D	%ΔRaw [C] mean (SD)
CORTISOL^a								
Log [C]	40	4.77 (0.42)	[4.63, 4.9]	40	5.08 (0.76) [*]	[4.84, 5.32]	0.51	64.41 (104.74)
Raw [C] (ng/ml)	40	128.66 (59.84)	[110.11, 147.2]	40	209.15 (147.87) [*]	[163.33, 254.98]	0.71	[30.91, 97.91]
CK-MM^a								
Log [C]	39	2.14 (0.66)	[1.93, 2.35]	39	2.32 (0.73) [*]	[2.09, 2.55]	0.26	40.24 (90.69)
Raw [C] (ng/ml)	39	11.36 (12.94)	[7.3, 15.43]	39	14.42 (18.05) [*]	[8.75, 20.08]	0.19	[10.84, 69.63]
COMP^a								
Log [C]	41	6.07 (0.33)	[5.97, 6.17]	41	6.17 (0.36) ^{**}	[6.06, 6.28]	0.28	15.22 (36.72)
Raw [C] (ng/ml)	41	457.04 (159.44)	[408.23, 505.84]	41	507.15 (180.49) ^{**}	[451.9, 562.4]	0.29	[3.64, 26.8]

^a significant for time^{*}POST-30 sample^{**}POST-0 sample

Table 6.4 - Raw (ng/ml), Natural Logarithm-Transformed, & %Δ for serum biomarker concentrations collapsed across groups pre and post-acute HTL.

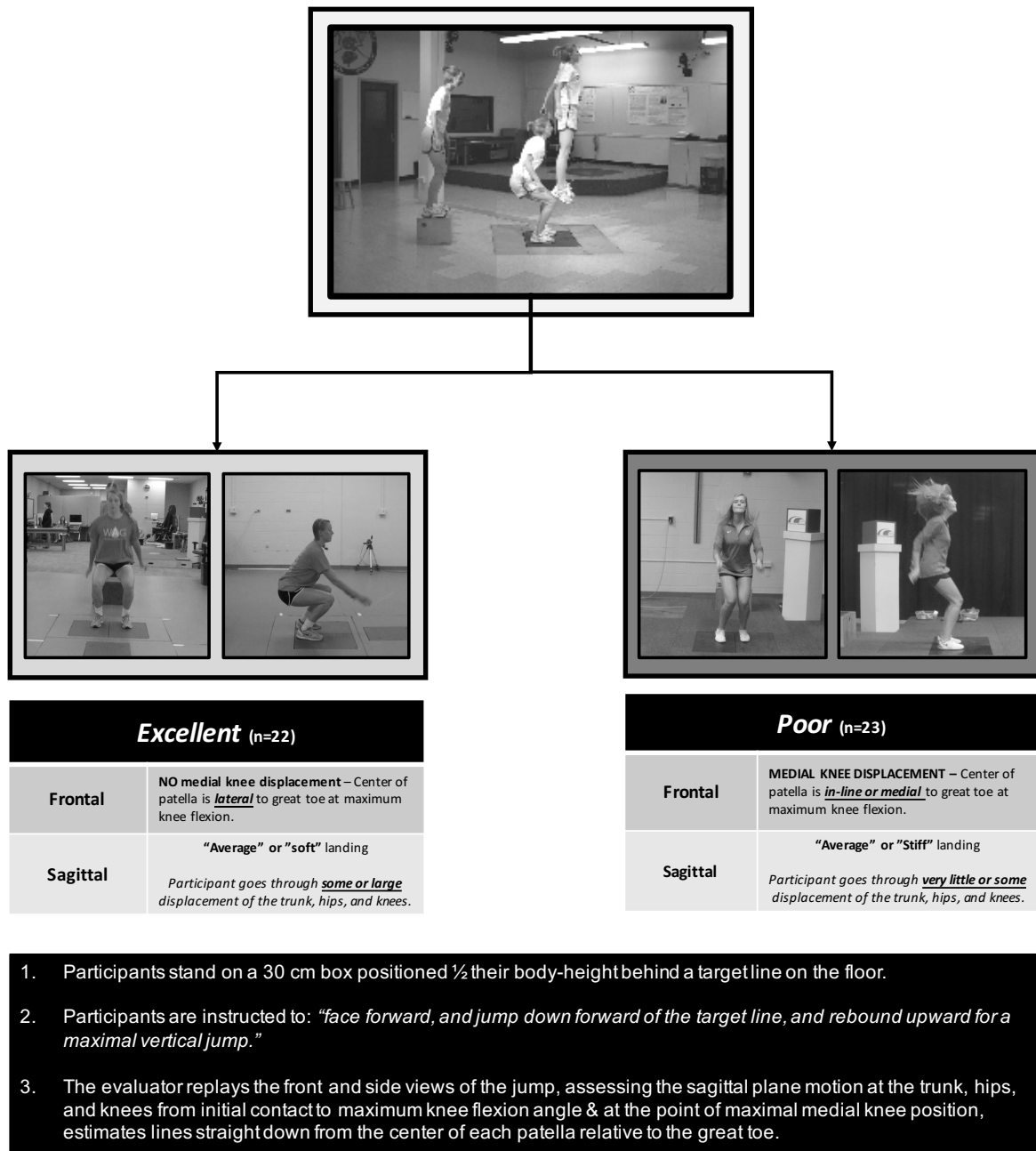


Figure 6.1 – Landing Error Scoring System Group Assignment Criterion.

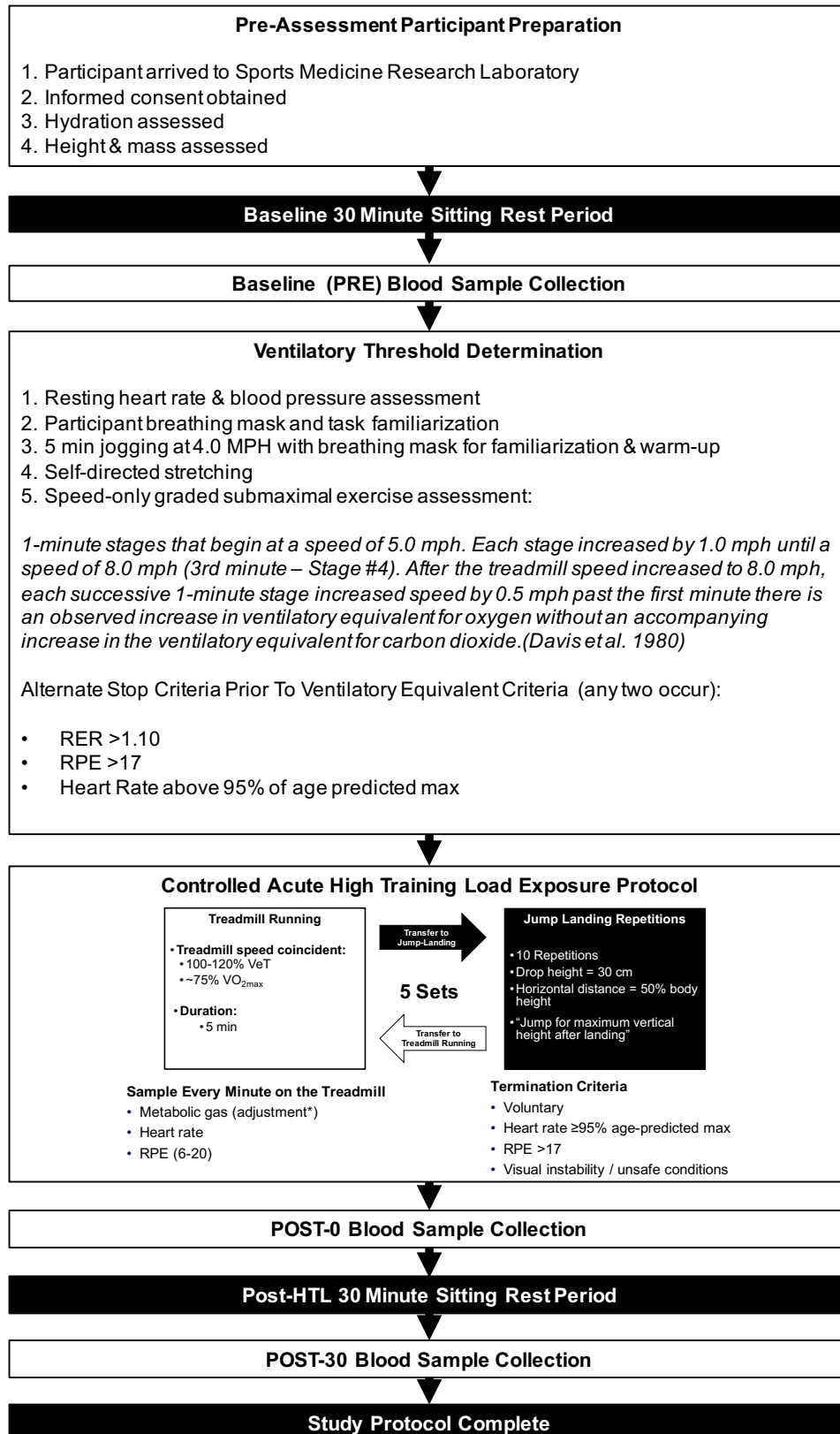


Figure 6.2 – Biomarker Assessment Testing Session Overview.

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APPENDIX 1. 17-Item LESS Operational Definitions

LESS Item	Operational Definition	Camera View	Error Condition	Score
<i>Stance width – Narrow</i>	Once the entire foot is in contact with the ground, draw a line down from the tip of the shoulders. If the line on the side of the test leg is outside of the foot then score less than shoulder width (narrow), score YES. If the test foot is internally or externally rotated, grade the stance width based on heel placement.	Front	Yes	Y=1 N=0
<i>Foot position - Toe In</i>	If the foot of the test leg is internally more than 30 degrees between the time period of initial contact and max knee flexion, then score YES. If the foot is not internally rotated more than 30 degrees between the time period of initial contact to max knee flexion, score NO.	Front	Yes	Y=1 N=0
<i>Foot position - Toe Out</i>	If the foot of the test leg is externally rotated more than 30 degrees between the time period of initial contact and max knee flexion, then score YES. If the foot is not externally rotated more than 30 degrees between the time period of initial contact to max knee flexion, score NO.	Front	Yes	Y=1 N=0
<i>Symmetric initial foot contact</i>	If one foot lands before the other or if one foot lands heel to toe and the other lands toe to heel, score NO. If the feet land symmetrically, score YES.	Side	No	Y=0 N=1
<i>Knee flexion displacement</i>	If the knee of the test leg flexes more than 45 degrees from initial contact to max knee flexion, score YES. If the knee of the test leg does not flex more than 45 degrees, score NO.	Side	No	Y=0 N=1
<i>Hip flexion at max knee flexion</i>	If the thigh of the test leg flexes more on the trunk from initial contact to max knee flexion angle, score YES.	Side	No	Y=0 N=1
<i>Trunk flexion at max knee flexion</i>	If the trunk flexes more from the point of initial contact to max knee flexion, score YES. If the trunk does not flex more, score NO.	Side	No	Y=0 N=1

APPENDIX 1. 17-Item LESS Operational Definitions

LESS Item	Operational Definition	Camera View	Error Condition	Score
<i>Knee valgus displacement</i>	At the point of max knee valgus on the test leg, draw a line straight down from the center of the patella. If the line runs through the great toe or is medial to the great toe, score YES. If the line is lateral to the great toe, score NO.	Front	Yes	Y=1 N=0
<i>Joint displacement</i>	Watch the sagittal plane motion at the hips and knees from initial contact to max knee flexion angle. If the subject goes through large displacement of the trunk, hips, and knees then score SOFT. If the subject goes through some trunk, hip, and knee displacement but not a large amount, then AVERAGE. If the subject goes through very little, if any trunk, hip, and knee displacement, then STIFF.	Side	Average or Stiff (double penalty for Stiff)	Soft=0 Average=1 Stiff=2
<i>Overall impression</i>	Score EXCELLENT if the subject displays a soft landing and no frontal plane motion at the knee, Score POOR if the subject displays a stiff landing and large frontal plane motion at the knee. All other landings, score AVERAGE.	Side, Front	Average or Poor (double penalty for Poor)	Excellent=0 Average=1 Poor=2

APPENDIX 2. Pre-Assessment Participant Guidelines

THE UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

Barnett Frank MA, ATC/LAT

Department of Exercise and Sport Science

209 Fetzer Hall, CB # 8700

(203) 512-4235 / bsfrank@email.unc.edu

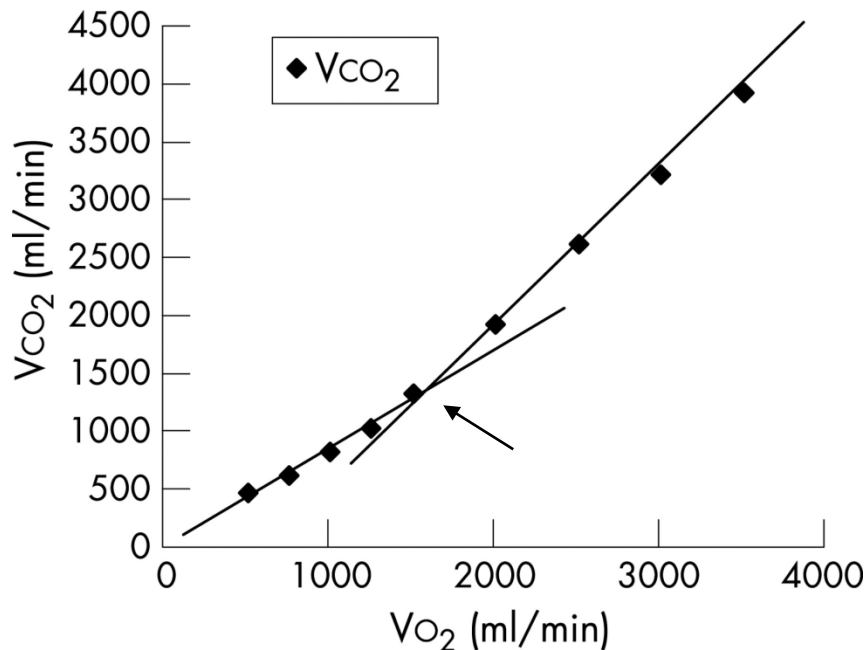
Pre-Test Guidelines

1. No eating 4 hours prior to testing.
2. Void completely before testing.
3. Maintain proper hydration prior to testing.
4. Please wear appropriate clothing/shoes for testing (running shorts/shirt/shoes)
5. No exercise 12 hours prior to testing.
6. No alcohol consumption 48 hours prior to testing.
7. No diuretic medications 7 days prior to testing.
8. No caffeine consumption 12 hours prior to testing.
9. Sleep at least 6 hours the night prior to testing.

Source: Advanced Fitness Assessment and Exercise Prescription – Third Edition – Vivian H. Heyward

APPENDIX 3. Modified “V”-Slope Method for Determination of Ventilatory Threshold

1. Carbon Dioxide output (VCO_2) is plotted against oxygen consumption (VO_2) as measured per minute during exercise.
2. A line with a slope of 1 is drawn through the points on the graph during the early phase of exercise.
3. The point on the line where VCO_2 departs drastically from VO_2 (break-away point) will be marked as the ventilatory threshold. The VO_2 value at this point will be recorded and reported as a percentage of $\text{VO}_{2\text{max}}$.



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