De Ste Croix, Mark B ORCID: 0000-0001-9911-4355, Elnagar, Youssif O, Iga, John, Ayala, Francisco and James, David V ORCID: 0000-0002-0805-7453 (2017) The impact of joint angle and movement velocity on sex differences in the functional hamstring/quadriceps ratio. Knee, 24. pp. 745-750. doi:10.1016/j.knee.2017.03.012

The impact of joint angle and movement velocity on sex differences in the functional hamstring/quadriceps ratio

Mark De Ste Croix PhD[1], Youssif O. ElNagar PhD1, John Iga PhD[2], Francisco Ayala PhD[3,4], David James PhD[1]

[1] Exercise and Sport Research Centre, School of Sport and Exercise, Faculty of Applied Sciences, University of Gloucestershire, UK.

[2]Wolverhampton Wanderers Football Club, Wolverhampton, UK

[3] Sports Research Centre, Miguel Hernández University of Elche, Alicante, Spain

[4] ISEN University Formation, Center affiliate to the University of Murcia, Murcia, Spain

Correspondence to: **Prof Mark De Ste Croix**

School of Sport and Exercise

University of Gloucestershire

Oxstalls Campus

Oxstalls Lane

Gloucester

GL2 9HW

Telephone: **+44 (0)1242 715159**

Fax: **+44 (0)1242715222**

Email: mdestecroix@glos.ac.uk

Word count: 3313

Abstract

Objective: Females are 2-8 times more likely to suffer a non-contact injury compared with males thus the purpose of this study was to explore the influence of joint angle and movement velocity on sex differences in the functional hamstring to quadriceps ratio (H/Q_{FUNC}).

Methods: Isokinetic concentric and eccentric torque were determined in 110 participants (55 males and 55 females) through a 90° range of movement at 60, 120, 240°/s. Testing was performed with the hip flexed at 10°. The H/Q_{FUNC} was determined at 3 specific joint angles (15, 30 and 45° flexion) and where peak torque occurred for concentric knee extension.

Results: A significant interaction effect ($P < 0.01$) for sex and joint angle was observed with women demonstrating a lower H/Q_{FUNC} than males, especially at more extended knee positions. A significant sex by velocity interaction ($P < 0.01$) indicated a lower H/Q_{FUNC} in women as velocity increased. Significant main effects ($P < 0.01$) indicated that irrespective of sex the H/Q_{FUNC} increased as the knee extends and velocity increases.

Conclusion: Given the reduced H/Q_{FUNC} in females compared to males at more extended knee positions and faster velocities, this may contribute to the observed sex bias in reported injury rates.

Keywords: injury risk, functional H/Q ratio, sex differences, joint angle, movement velocity

1. Introduction

It is well recognised that based on hours of exposure to sporting activity females are more likely to suffer a non-contact ACL injury compared to males [1] with the proposed mechanisms for this increased relative risk multifactorial [2]. It has been suggested that irrespective of sex it is important that the muscles produce efficient muscular control to provide compression to maintain joint stability (dynamic stability), by co-activating and producing joint stiffness and net joint moment [3]. Their co-activation improves joint stiffness and decreases ACL strain [4], however, functional stability changes during movement since both static and dynamic stability are affected by joint angle and movement velocity. Previous studies have identified a link between injury incidence, especially ACL rupture, and low hamstring to quadriceps ratios, indicating that compromised H/Q ratios are a risk factor for injury [5,6].

The functional ratio (H/Q_{FUNC}) (Eccentric Hamstrings / Concentric Quadriceps) has been proposed to appropriately reflect co-contraction of the limb [3,7] but despite a growing literature base exploring the H/Q_{FUNC} little regard has been given to joint angle specific determination of the ratio. Most studies divide the velocity specific eccentric peak torque value for the hamstrings by the concentric peak torque value for the quadriceps [8-11]. However, this method of determination lacks functional relevance as it does indicate co-contraction capability of the muscle around the joint. Simply using peak torque also fails to examine the ratio at joint angles where injury is most likely to occur (e.g 0-30° of knee flexion). Peak torque values for the hamstrings and quadriceps during concentric and eccentric muscle actions occur during the mid-range of the movement and previous studies have demonstrated that the muscle specific torque generating capability during concentric and eccentric actions are altered at decreased joint angles [12,13]. An additional problem of using peak torque values to calculate the H/Q_{FUNC} ratio is that concentric and eccentric PT will most likely not occur at the same joint angle.

Only a few studies appear to have examined the angle specific H/Q_{FUNC} ratio using small sample sizes, from males only, and do not all include joint angles near full knee extension [3,14,15]. However, these studies have reported an increase in the H/Q_{FUNC} as the knee approaches extension with one reporting ratios as high as 3.14 at 180º /s in pubertal males [16]. Current data would suggest that muscular control of the knee is highly dependent upon the angular position examined in males however, it remains to be established if this is similar in females. Determination of the H/Q_{FUNC} at more extended knee positions may be more important for females seeing as biomechanical analysis indicates that females tend to land with the knees in more extended joint positions [17]. Additionally, studies determining the H/Q_{FUNC} have tended to determine torque in a seated position with the hip flexed (80-90° of flexion). It is well recognised that injury is most likely to occur when the hip is extended (around 10° of hip flexion) and therefore determination of torque with the hip flexed might be considered not functionally relevant. For example, a recent study indicated that the H/Q_{FUNC} is significantly lower when the hip is flexed at 10° compared with 80° [18].

A number of studies have examined changes in the H/Q_{FUNC} with increasing velocity and as peak torque has been used to calculate the H/Q_{FUNC} most studies have demonstrated a significant increase in the ratio with increasing velocity [7,10,16]. This is attributed to the decrease in concentric force production with increasing velocity compared to the plateauing of torque production with increasing velocity during eccentric actions. However, whether this relationship remains when the H/Q_{FUNC} is calculated using angle specific data remains to be identified. This muscular control of the knee during fast velocity movements (such as sprinting) has important implications for injury risk.

Data exploring sex differences in the H/Q_{FUNC} are conflicting [7,19,20] and may be related to the different age ranges and training background of participants. Others have suggested that sex differences in H/Q_{FUNC} are generally observed only at high knee angular velocities that approach those during sports activities [21]. These data suggest that muscular control of the knee during fast extension movements may be less optimal in females compared to males, but this hypothesis requires investigation at joint angles where injury is likely to occur.

The combination of hip position, joint angle and movement velocity may all have a cumulative effect on sex differences in muscle control since both static stability and neuromuscular function can be affected. Thus, the purpose of this study was to examine the effect of joint angle and movement velocity on sex differences in the H/Q_{FUNC}.

2. Material and Methods

2.1 Participants

One hundred and ten participants, consisting of 55 males (age = 29 ± 5 y; stature = 1.81 ± 0.07 m; body mass = 82 ± 7 kg) and 55 females (age = 27 ± 6 y; stature = 1.61 ± 0.08 m; body mass = 68 ± 9 kg) who were recreationally active adults (engaging in 2-5 hours of moderate physical activity 3-5 days per week, but not involved in systematic sports training) completed the study. Participants were instructed to avoid their regular training regimens throughout the experimental period and not to take part in any vigorous physical activity 48 hours preceeding each testing day. There were 4 exclusion criteria in this study: (1) previous surgery of the knee (2) histories of orthopaedic problems, such as episodes of hamstrings injuries, fractures, surgery or pain in the spine or hamstring muscles over the past six months; (3) evidence of self-reported delayed onset muscle soreness (DOMS) at a testing session; and (4) for female participants being in the luteal phase of the menstrual cycle which was self-reported by the participant. None of the participants reported any form of musculoskeletal disorder at the time of testing. The participants were verbally informed about the study procedures before testing and provided written informed consent. The study was approved by the University's Research Ethics Committee. Participants visited the laboratory one week prior to testing to familiarise themselves with the laboratory and the experimental procedures.

2.2 Isokinetic assessment

A Biodex System-3 Isokinetic dynamometer (Biodex Corp., Shirley, NY, USA) and its respective manufacture software were used to determine peak torque during knee extension and flexion movements. The dynamometer was calibrated according to the manufacturer's instructions before the start of each test session.

Testing began with a standardised warm up consisting of 5 minutes of cycling at 60W on a Monark cycle ergometer 814E (Varberg, Sweden). Two minutes after the warm up was completed, maximal concentric and eccentric isokinetic peak torque for knee flexion and extension of the dominant leg, determined through interview and defined as the leg preference when kicking a ball was tested. Participants were secured in a prone position on the dynamometer with the hip passively flexed at 10º and the body head was maintained at 0º of flexion. The axis of rotation of the dynamometer lever arm was aligned with the lateral epicondyle of the knee and the seat length was adjusted so that the participant`s patella was approximately 2-4 cm away from the edge of the seat. The force pad was placed approximately 3 cm superior to the medial malleolus with the foot in a relaxed position. Adjustable strapping across the pelvic, posterior thigh proximal to the knee and foot localised the action of the musculature involved. The range of movement was set from 0° (0º was determined as maximal voluntary knee extension for each participant) to 90° knee flexion using a twin axis electrogoniometer (Biometrics, UK). All settings, including seat height, seat length, dynamometer height and lever arm length, were noted during the familiarization session so that they were identical through experimental trials. During the isokinetic testing procedure, the cushion setting on the control panel for the ends of the range of motion was set to its lowest (hardest) setting in order to reduce the effect of limb deceleration on the reciprocal motion. The prone position (10º hip flexion) was selected instead of a seated position (80-110º hip flexion) for two main reasons: (a) the prone position is more functionally representative of the hip position during running/sprinting and landing in contrast with a seated position; and (b) a prone position replicates the knee flexor and extensor muscle length-tension relationships which occurs in the late phase and the early contact phase of sprinting.

Concentric/concentric (CON/CON) cycles were performed first during continuous extension/flexion movements with extension always undertaken first. This was followed after 5 min of rest by eccentric/eccentric (ECC/ECC) actions. For both muscle actions, three cycles of knee flexions and extensions were performed at three preset constant angular velocities in the following order: 60, 120 and 240º/s (slow to fast) with 30s rest between velocities. The passive eccentric mode was chosen so that the full range of movement would be completed for every action. For both CON/CON and ECC/ECC cycles, participants were encouraged to push/resist as hard and as fast as possible and to complete the full range of motion. Participants were told to abort the test if they felt any discomfort or pain. During the test, all participants were verbally encouraged by the investigator to give their maximal effort, and the instructions were standardized by using key words such as “resist”, “push/pull” and “hard and fast as possible”. The H/Q_{FUNC} ratio was determined for each velocity by dividing eccentric hamstrings torque by concentric quadriceps torque using 4 angle specific torque values using the highest torque achieved from the 3 repetitions. These were 15, 30 and 45° of knee flexion and using the angle of maximal PT obtained during concentric quadriceps action for each velocity.

2.3 Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (v22.0). Firstly the distribution of raw data sets was checked for homogeneity and skewness using the Kolmogorov-Smirnov test. Descriptive statistics including means and standard deviation were calculated for each measure. A 2 (sex) x 4 (joint angle) x 3 (movement velocity) analysis of variance was undertaken to determine the influence of joint angle and movement velocity on sex differences in the $H/Q_{FUNC.}$ Significant interaction and main effects were further examined using Bonferroni-corrected post hoc *t*-tests. The level of significance was set at $P \leq 0.05$ for all tests.

3. Results

H/Q_{FUNC} by sex, velocity and joint angle can be seen in Figures 1 and 2 For the H/Q_{FUNC} ratio at 60°/s, 120°/s and 240°/s, a statistically significant interaction ($F_{(3, 108)} = 4.310$, $p < 0.01$) was observed between knee joint angle and sex. Post hoc analysis revealed that the H/Q_{FUNC} ratio was significantly lower at 15° and 30° in females compared to males, but not at 45° or where PT occured. A significant main effect ($p < 0.05$) for sex was observed for all knee joint angles irrespective of movement velocity with the H/Q_{FUNC} ratio higher for males than females. A significant main effect ($F_{(3, 108)} = 191.195$, $p < 0.01$) for knee joint angle was observed irrespective of sex and movement velocity, with the H/Q_{FUNC} ratio significantly lower at 15° compared to 30°, 45° and where PT occurred.

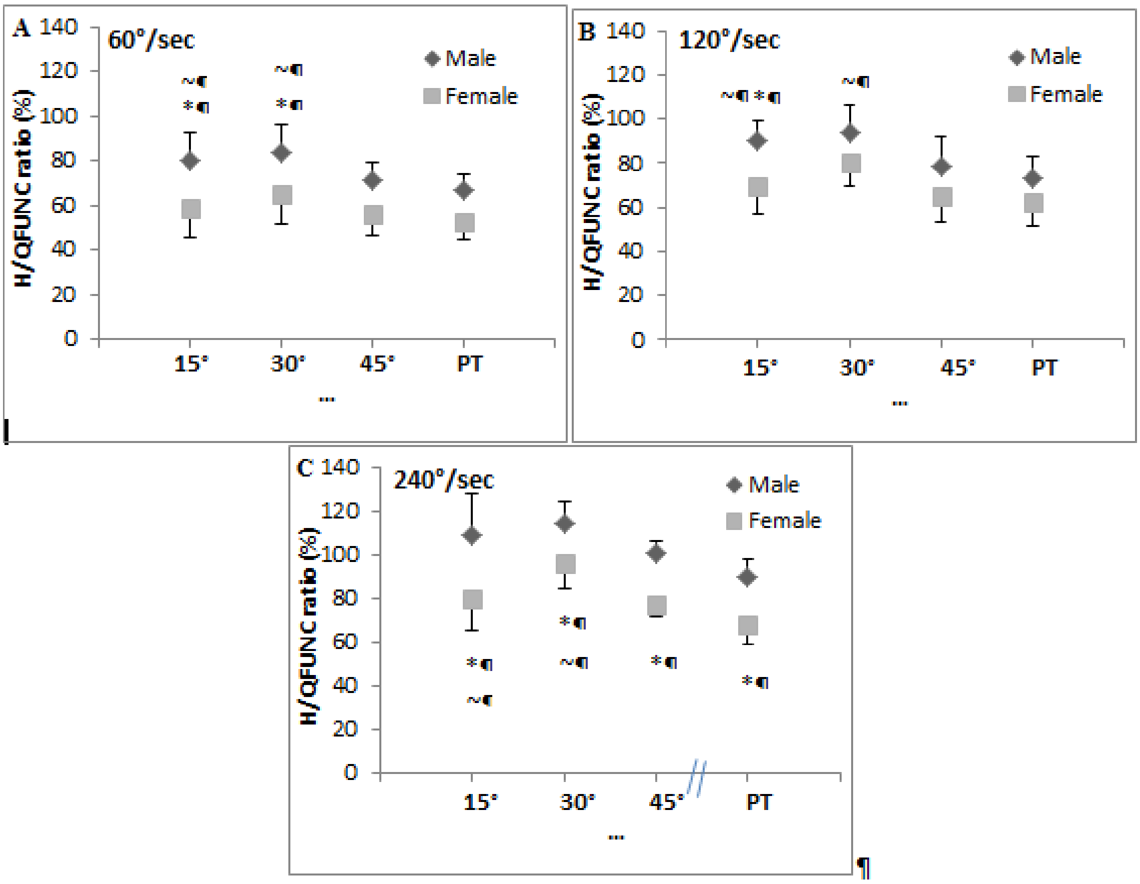

FIGURE 1: H/Q_{FUNC} ratio at 60°/s (panel A), 120°/s (panel B) and 240°/s (panel C) across joint angle (15º, 30º and 45º and PT) for males and females. (* significant sex difference p<0.05; ~ significant difference in joint angle p<0.05)

A statistically significant interaction was also observed between angular velocity and sex ($F_{(6, 108)} = 6.244$, $p < 0.01$). Post hoc analysis also revealed that the H/Q_{FUNC} ratio was significantly lower in females compared to males at 120°/s and 240°/s but not at 60°/s. A significant main effect ($F_{(2, 108)} = 398.711$, $p < 0.01$) for angular velocity was observed for each knee joint angle, irrespective of sex, where H/Q_{FUNC} ratio increased with increased angular velocity.

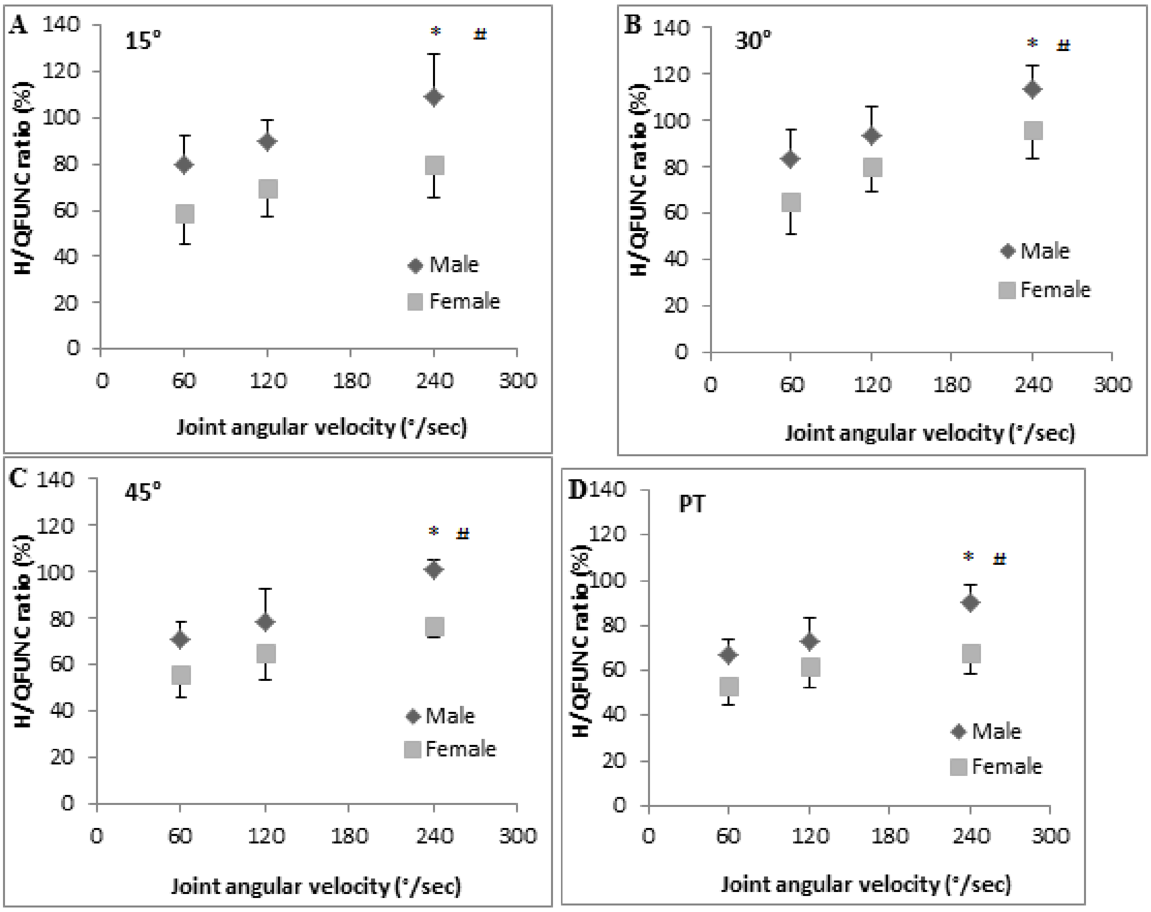

FIGURE 2: H/Q_{FUNC} ratios at 15º (panel A), 30º (panel B), 45º (panel C) and PT (panel D) for males and females across joint angular velocities (60°/s, 120°/s and 240°/s) (*significant sex difference $p<0.05$; # significant main effect for joint angular velocity $p<0.05$)

4. Discussion

Previous studies have suggested that females with decreased hamstrings relative to the quadriceps peak torque may be at increased relative risk of injury [22]. However, the majority of previous data must be viewed with a degree of caution as most previous studies have: a) failed to explore sex differences in the H/Q_{FUNC} ratio using angle specific torque values where injury is most likely to occur; and b) have determined torque in a seated position with the hip flexed. The findings of the current study demonstrated a statistically significant interaction between joint angle and sex for the H/Q_{FUNC} ratio. This interaction indicates that the H/Q_{FUNC} ratio of males and females increases closer to full knee extension but is lower in females compared to males.

To our knowledge this is the first study to have reported significant sex differences in the H/Q_{FUNC} ratio using an angle specific ratio. By using angle specific data we have also been able to demonstrate that the sex difference in the relative angle-specific maximal force producing capability increases as the knee joint moves towards full knee extension. This is attributed to lower eccentric torque production of hamstring muscles compared with concentric torque production of quadriceps muscles as the knee extends in females, compared to males. Although the H/Q_{FUNC} ratio increase as knee moves towards full knee extension our findings are considerably lower than those data that have previously reported angle specific H/Q_{FUNC} ratios [16]. Kellis and Katis [16] reported greater H/Q_{FUNC} ratio values at 0-10° of knee flexion compared to the data in the current study. The reason why we may have found differences compared to the Kellis and Katis [16] study is that they average torque over 10° portions of the movement whereas we used a single angle specific torque value. Testing in the Kellis and Katis [16] study was also conducted in a seated position and we have previously reported that the H/Q_{FUNC} ratio is significantly higher in seated versus a supine position by as much as 21% at faster movement velocities [3.14 $rad \cdot s^{-1}$] [18]. Within the literature it is often cited that a H/Q_{FUNC} ratio of outside the 0.7-1 range suggests an increase in the injury risk [23]. It is important to consider that the H/Q_{FUNC} of 1.0 cited as being representative of producing 'adequate' knee muscle control is based on a value determined using PT and thus from the mid-range of movement. Based on previous studies the functional ratios of below 1.0 for the females in the current study may be attributed to the inability to recruit their entire motor unit pool during eccentric actions, but caution must be taken here as we have not directly measured motor unit activation. According to the current findings showing significant sex differences, injury risk in females may be greater than that of males, due to specific eccentric hamstring weakness when the joint is approaching full extension and with increasing angular velocity. This could possibly represent the inability of the hamstrings to absorb the anterior tibial forces induced by the concentric quadriceps action [3,13], although it should be remembered that isokinetic testing occurs at a fixed movement velocity. However, this potentially has implications for dynamic knee stability near full knee extension and in particular reinforces the need to examine the ratio closer to full knee extension and over a range of movement velocities.

In the current study, at decreased joint angles (closer to full knee extension) the H/Q_{FUNC} ratio at all three angular velocities was increased due to a larger decrease in the quadriceps concentric torque than in eccentric hamstrings torque and is in agreement with previous findings [2,15,16]. The current data support previous work on male footballers that reported that the H/Q_{FUNC} at PT was 0.78 compared with over 1.5 near full knee extension [15]. It would appear that this protective mechanism is important, as landing that occurs with a knee angle of less than 30° of flexion places greater load on the ACL compared to landing in more flexed knee positions [24]. In the current study during fast knee extension movements the H/Q_{FUNC} increased with extended joint angle position, indicating a significant capacity of the hamstring muscles to provide dynamic joint control in these conditions. Thus the data of current study support the literature indicating that the H/Q_{FUNC} is enhanced near full knee extension and reinforce the need to evaluate H/Q_{FUNC} ratios at joint angles across the range of movement and especially towards full knee extension.

The reduction in strength that evidenced in the current study by a decline in concentric compared to eccentric torque with increasing angular velocity is in agreements with previous studies [15,25]. Our results support those observations which have reported that the quadriceps posses' greater concentric torque than the eccentric hamstring muscles at all angular velocities. Hewett et al. [21] reported similar velocity related effects to that of the current study, albeit using the conventional H/Q. However, in contrast to the current study they only found sex differences at faster testing velocities. The significant sex by velocity interaction effect observed in the current study indicates that irrespective of joint angle position the sex difference in the H/Q_{FUNC} ratio increased with increasing movement velocity. These data suggest that compared to males females have a reduced capacity to control the joint during fast velocity movements which is required to stabilise the joint and protect the anterior cruciate ligament [21]. These findings suggest that movement velocity may be a risk factor in the relative risk of ACL and hamstring injury in female athletes.

The findings of current study support previous observations which have reported a higher H/Q_{FUNC} ratio in males compared with females [21,26,27]. This may be due to the proposed quadriceps dominance seen in females quadriceps and/or lower eccentric hamstring torque generating capability compared with males. This reduced ability to co-activate the hamstrings during concentric quadriceps actions has important implications as it provides protection to the knee joint not only against excessive anterior drawer, but also against knee abduction and dynamic lower extremity valgus [28].

5. Conclusion

The findings of the current study would suggest that the ability of the muscles to control the joint are influenced by sex, joint angle, and movement velocity. The significant decrease in the H/Q_{FUNC} ratio close to full knee extension and with increased angular velocity, demonstrates compromised muscular control of the joint and has implications in injury risk. The significant sex difference observed in the current study further identifies females at risk, especially during movements where it is recognised that they flex the knee less than males (for example during landing) [28]. These data reinforce the need to focus on both increasing hamstring eccentric strength and landing mechanics training for females involved in activities that use such movements and on eccentric hamstring conditioning near full knee extension.

References

1. Beynnon BD, Vacek PM, Newell MK, Tourville TW, Smith HC, Shultz SJ, et al. The effects of level of competition, sport, and sex on the incidence of first-time noncontact anterior cruciate ligament injury. Am J Sports med 2014;42:1806-12.
2. Griffin LY, Albohm MJ, Arendt EA, Bahr R, Beynnon BD, DeMaio M, et al. Understanding and Preventing Noncontact Anterior Cruciate Ligament Injuries A Review of the Hunt Valley II Meeting, January 2005. Am J Sports Med 2006;34:1512-32.
3. Aagaard P, Simonsen EB, Andersen JL, Magnusson SP, Bojsen-Moller F, Dyhre-Poulsen P Antagonist muscle coactivation during isokinetic knee extension. Scand J Med Sci Sports 2000;10:58-67.
4. More RC, Karras BT, Neiman R, Fritschy D, Woo SL, Daniel DM. Hamstrings—an anterior cruciate ligament protagonist An in vitro study. Am J Sports Med 1993;21:231-7.
5. Söderman K, Alfredson H, Pietilä T, Werner S. Risk factors for leg injuries in female soccer players: a prospective investigation during one out-door season. Knee Surg, Sports Trauma, Arthro. 2001;9:313-21.
6. Holcomb WR, Rubley MD, Lee HJ, Guadagnoli MA. Effect of hamstring-emphasized resistance training on hamstring: quadriceps strength ratios. J Streng Condit Res 2007;21:41-7.
7. De Ste Croix MBA, Deighan MA, Armstrong N Functional eccentric-concentric ratio of knee extensors and flexors in pre-pubertal children, teenagers and adults. Int J Sports Med 2007;28:768-72.
8. Delextrat A, Gregory J, Cohen D. The use of the functional H: Q ratio to assess fatigue in soccer. Int J Sports Med 2010;31:192-7.
9. Greig M. The influence of soccer-specific fatigue on peak isokinetic torque production of the knee flexors and extensors. Am J Sports Med 2008;36:1403-9.

10. Oliveira ADSC, Caputo F, Gonçalves M, Denadai BS. Heavy-intensity aerobic exercise affects the isokinetic torque and functional but not conventional hamstrings: quadriceps ratios. J Electro Kinesio 2009;19:1079-84.
11. Small K, McNaughton L, Greig M, Lovell R. The effects of multidirectional soccer-specific fatigue on markers of hamstring injury risk. J Sci Med Sport 2010;13:120-5.
12. Klass M, Guissard N, Duchateau J. Limiting mechanisms of force production after repetitive dynamic contractions in human triceps surae. J Appl Physiol 2004;96:1516-21.
13. Komi PV, Linnamo V, Silventoinen P, Sillanpää, M. Force and EMG power spectrum during eccentric and concentric actions. Med Sci Sports Exerc 2000;32:1757-62.
14. Aagaard P, Simonsen EB, Magnusson SP, Larsson B, Dyhre-Poulsen P A new concept for isokinetic hamstring: quadriceps muscle strength ratio. Am J Sports Med 1998;26:231-237.
15. Evangelidis PE, Pain MTG, Folland J. Angle-specific hamstring-to-quadriceps ratio: A comparison of football players and recreationally active males. J Sports Sci 2015;33:309-19
16. Kellis E, Katis A Quantification of functional knee flexor to extensor moment ratio using isokinetics and electromyography, J Athl Train 2007;42:477-86.
17. Hass C, Schick E, Tillman M, Chow J, Brunt D, Cauraugh J Knee biomechanics during landings: Comparison of pre and post-pubescent females. Med Sci Sports Exer 2005;37:100-7.
18. Deighan MA, Serpell BG, Bitcon MJ, De Ste Croix MBA Knee joint strength ratios and effects of hip position in Rugby players. J Stren Condit Res 2012;26(7):1959-66.
19. Bojsen-Moller J, Larsson B, Magnusson S. P, Aagaard P. Yacht type and crew-specific differences in anthropometric, aerobic capacity, and muscle strength parameters among international Olympic class sailors. J Sports Sci 2007;25:1117-28.

20. Kong PW, Burns SF. Bilateral difference in hamstrings to quadriceps ratio in healthy males and females. Phys Ther Sport 2010;11:12-7.

21. Hewett TE, Myer GD, Zazulak BT Hamstrings to quadriceps peak torque ratios diverge between sexes with increasing isokinetic angular velocity. J Sci Med Sports 2008;11:452-8.

22. Knapik JJ, Bauman CL, Jones BH, Harris JM, Vaughan L Preseason strength and flexibility imbalances associated with athletic injuries in female collegiate athletes. Am J Sports Med 1991;19**:**76-81.

23. De Ste Croix, MBA, Deighan MA Dynamic knee stability during childhood. In: De Ste Croix M and Korff T. editors. *Paediatric biomechanics and motor control: Theory and application* UK. Routledge, 2011 p. 233-58

24. Myers CA, Hawkins D Alterations to movement mechanics can greatly reduce anterior cruciate ligament loading without reducing performance. J Biomech 2010;43**:**2657-64.

25. Westing SH, Seger JY. Eccentric and concentric torque-velocity characteristics, torque output comparisons, and gravity effect torque corrections for the quadriceps and hamstring muscles in females. Int J Sports Med 1989;10:175-80.

26. Calmels PM, Nellen M, Van Der Borne I, Jourdin P, Minaire P Concentric and eccentric isokinetic assessment of flexor-extensor torque ratios at the hip, knee, and ankle in a sample population of healthy subjects. Arch Phys Med Rehabil 1997;78**:**1224-30.

27. Yoon TS, Park DS, Kang SW, Chun SI, Shin JS Isometric and isokinetic torque curves at the knee joint. Yonsei Med J 1991;32**:**33-43

28. Hewett TE, Myer GD, Ford KR Anterior cruciate ligament injuries in female athletes part 1, mechanisms and risk factors. Am J Sports Med 2006;34:299-311.

Authors Contributions

All authors provided input into the rationale and review of literature. YEN and MDSC designed the study and YEN collected all data. YEN and FA undertook the statistical analysis. All authors contributed to the interpretation of the data, the drafting and writing of the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing Interests

None of the authors declare competing financial interests

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.