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Pfeifer, Craig E. ORCID logoORCID: <https://orcid.org/0000-0002-0635-4956>, Beattie, Paul F, Sacko, Ryan S and Hand, Amy (2018) Risk factors associated with non-contact anterior cruciate ligament injury: a systematic review. International Journal of Sports Physical Therapy, 13 (4). pp. 575-587. doi:10.26603/ijsp20180575

Official URL: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6088120/>
DOI: 10.26603/ijsp20180575
EPrint URI: <https://eprints.glos.ac.uk/id/eprint/6993>

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RISK FACTORS ASSOCIATED WITH NON-CONTACT ANTERIOR CRUCIATE LIGAMENT INJURY: A SYSTEMATIC REVIEW

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ABSTRACT

Background: With the increasing number of individuals participating in sports every year, injury - specifically anterior cruciate ligament (ACL) injury - remains an inherent risk factor for participants. The majority of ACL injuries occur from a non-contact mechanism, and there is a high physical and financial burden associated with injury. Understanding the risk factors for ACL injury may aid in the development of prevention efforts.

Purpose: The purpose of this review was to synthesize and appraise existing literature for risk factors associated with non-contact anterior cruciate ligament (ACL) injury in both sexes.

Study Design: Systematic review.

Methods: An electronic literature search was conducted utilizing the MEDLINE database and The Cochrane library for articles available through February 2016. All titles and abstracts were reviewed and full text articles meeting eligibility criteria were assessed in detail to determine inclusion or exclusion. Articles reviewed in full text were reviewed for scientific evidence of risk factors for ACL injury. Results from studies were extracted and initially classified as either intrinsic or extrinsic risk factors, and then further categorized based upon the evidence presented in the studies meeting inclusion criteria. Data extracted from eligible studies included general study characteristics (study design, sample characteristics), methodology, and results for risk factors included.

Results: Principal findings of this systematic review identified the following risk factors for ACL injury in both sexes: degrading weather conditions, decreased intercondylar notch index or width, increased lateral or posterior tibial plateau slope, decreased core and hip strength, and potential genetic influence.

Conclusions: Neuromuscular and biomechanical risk factors may be addressed through neuromuscular preventative training programs. Though some extrinsic and other inherent physiological factors tend to be non-modifiable, attempts to improve upon those modifiable factors may lead to a decreased incidence of ACL injury.

Level of Evidence: 2a.

Key Words: anterior cruciate ligament, ACL, risk factor, injury, rupture.

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The authors of this manuscript have no conflict of interests to report.

INTRODUCTION

Over 212 million individuals worldwide participate in competitive or leisure time sports activities.¹ There is an inherent risk of injury for sport participants, due to the nature of competition and the physiological requirements placed on the body.²⁻⁴ While contact may play a factor, over 70% of anterior cruciate ligament (ACL) injuries occur with a non-contact mechanism,⁵⁻⁷ with an estimated 100,000 injuries per year within the National Collegiate Athletic Association (NCAA) alone.⁸ A review of ACL injuries from the NCAA revealed that the highest rate of injury in men occurred in football (0.17 per 1000 Athlete-Exposures [A-E]), while for women, basketball and lacrosse show the highest rate of injury (0.23 per 1000 A-E).⁹ Surgical reconstruction stands as the most common treatment option for complete ACL rupture.¹⁰ The cost of ACL injury comes in the form of lost participation time as well as monetary cost of reconstructive surgery. The cost of a reconstructive ACL surgery averages \$12,740,¹⁰ with lifetime societal costs (e.g. disability, decreased productivity) upwards of \$38,000.¹¹

Due to the high individual and societal costs associated with ACL injury, and the catastrophic impact to an individual's quality of life, prevention of this condition should continue to be a primary concern. Prevention begins with an understanding of risk factors associated with ACL injury. Risk factors that predispose an individual for injury are categorized as intrinsic or extrinsic. Intrinsic factors, those inherent to the individual, are further subdivided as either modifiable or non-modifiable. Modifiable risk factors are those that may be altered in the individual (e.g. muscular strength or flexibility). Non-modifiable risk factors include those which are intrinsic and cannot be controlled by the individual (e.g. anatomical structure).¹² Extrinsic risk factors are those that are outside of the control of the individual (e.g. playing surface). Due to extrinsic and non-modifiable intrinsic factors, the risk of ACL injury will always exist. The opportunity to reduce the prevalence of ACL injury may be achieved by employing preventative measures derived from the knowledge of modifiable risk factors.^{13,14} Currently, preventative programs have shown promise for the reduction of ACL injury risk in sport.^{13,14} Previously,

systematic reviews have addressed the risk factors associated with only one sex,^{15,16} with insignificant cross comparison. Aggregating the current literature of risk factors for ACL injury for both sexes provides the unique opportunity to address factors across the population, and to identify those that require more individualistic approaches. Therefore, the purpose of this systematic review was to synthesize and appraise existing literature for risk factors associated with non-contact ACL injury in both sexes.

METHODOLOGY

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement for systematic reviews was utilized for reporting in this study.¹⁷ Initial criterion for inclusion in this review was observational, prospective, or retrospective human studies which investigated risk factors for injury to the ACL. Additional inclusion criteria included those written in the English language and those with a level of evidence between I and IV.¹⁸ Studies that did not utilize non-contact ACL injury as an outcome or did not use ACL injured participants were excluded. Studies identifying secondary or tertiary factors related to ACL injury were excluded. Both diagnostic and therapeutic studies were excluded; i.e. studies investigating roles of preventative interventions investigating potential risk reduction. Studies that did not present significant findings of association of risk from potential factors were excluded. Previous systematic review, meta-analyses, and review articles were excluded. Studies not written in the English language were excluded, and there were no population restrictions utilized during the search.

Data Sources

An electronic literature search was conducted utilizing the MEDLINE database and The Cochrane library for all articles available through February 2016. The literature search was conducted utilizing search strategies (inclusion & exclusion) and keywords modeled from prior systematic reviews, and these are summarized in Table 1.¹⁵

Study Selection & Data Extraction

All titles and abstracts were reviewed and full text articles meeting eligibility criteria were assessed in

Table 1. *Systematic search strategies and keywords.*

Database	Search	Keywords
Pubmed	1	(risk) OR risk of
	2	(injury OR injuries OR tear OR tears OR tearing OR rupture OR rupture OR sprain OR sprains)
	3	(anterior cruciate ligament or ACL)
	4	(((((prospective) OR randomized controlled trial) OR cohort) OR Case control) OR case-control) OR longitudinal
	5	#1 AND #2 AND #3 AND #4
	6	reconstruction
	7	#5 NOT #6
	8	(animals) NOT (animals AND humans)
	9	#7 NOT #8
	10	((editorial) OR letter) OR comment)
	11	#9 NOT #10
	12	#9 NOT #10: Filters: English
Cochrane	1	(risk) OR risk of
	2	MeSH descriptor: [Anterior Cruciate Ligament] explode all trees
	3	anterior cruciate ligament OR ACL (word variations have been searched)
	4	#2 or #3
	5	MeSH descriptor: [Wounds and Injuries] explode all trees
	6	injuries OR injury OR tear OR tears OR tearing OR rupture OR ruptures OR sprain OR sprains (word variations have been searched)
	7	#5 or #6
	8	prospective OR randomized controlled trial OR cohort OR case control OR case-control (word variations have been searched)
	10	animals NOT (animals AND humans)
	11	editorial OR letter OR comment
	12	#1 AND #4 AND #7 AND #8 NOT #10 NOT #11

detail to determine inclusion or exclusion. Abstracts and articles were reviewed for inclusion by two authors, and upon any discrepancies, a third author would provide a ruling. The search of the literature resulted in a total of 381 references; of which one was a duplicate and another 301 studies were excluded (Figure 1). A total of 79 full text articles were reviewed, 55 of which met criteria for inclusion and were subsequently incorporated. Articles reviewed in full text were reviewed for the presence of inclusion criteria, specifically for scientific evidence of risk factors for potential ACL injury. Results from studies were extracted and initially classified as either intrinsic or extrinsic risk factors. Extrinsic risk factors were further categorized in to weather, playing surface, sport level, ski type,

and participation level. Intrinsic risk factors were labeled as anatomical, neuromuscular, biomechanical, physiologic, and genetic.¹⁵ Data extracted from eligible studies included general study characteristics (study design, sample characteristics), methodology, and results for risk factors included.

Assessment of quality

Assessment of risk of bias for the studies included was performed utilizing previously established criteria from Alentorn-Geli et al. (Table 2).¹⁵ A quality score was assigned for each study included, utilizing each 'yes' as one point toward the studies score and other responses receiving no points.¹⁵ Higher quality scores indicated studies with a greater methodological rigor.

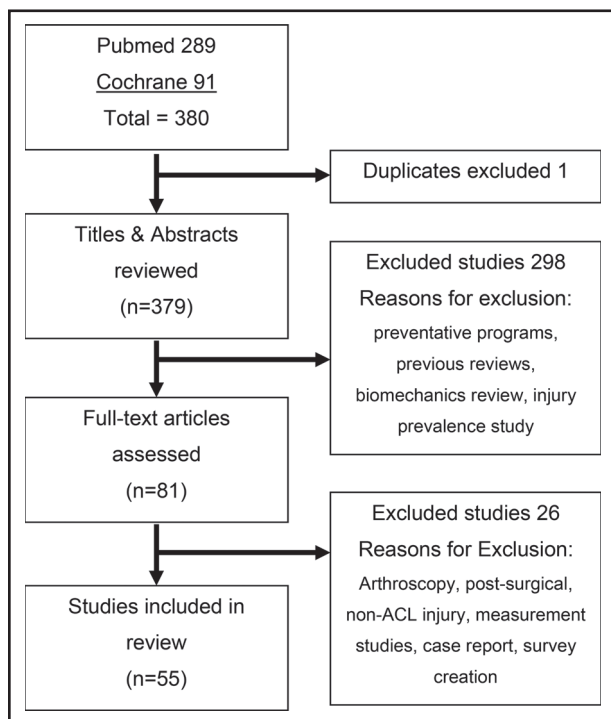


Figure 1. PRISMA Diagram.

RESULTS

Summary of risk of bias

In general, studies involved in this systematic review appear to have a moderate risk of bias. Of the involved studies, there was a high proportion of unreported information relating to the assessment of risk of bias and quality score.

Extrinsic Risk Factors

There were a total of 10 risk factors identified which were subsequently categorized as extrinsic: five related to weather, two to playing surface, one sport level, one ski type, and one participation level (Table 3).

Three studies identified risk factors for ACL injury stemming from weather conditions. Two studies by Orchard et al.^{19,20} examined the weather conditions surrounding matches of Australian football over several years of match play. It was determined that a high evaporation rate for 28 days leading up to the match date placed individuals at a higher risk for injury (RR=2.8).¹⁹ Both studies reported that low rainfall in the year preceding matches increased the risk of injury (RR=1.5 to 1.93).^{19,20} Additionally, the absence of rainfall during matches placed those playing at a higher risk of injury (RR=1.55).²⁰ The last

weather-related study reported female recreational skiers were at an increased risk of injury while in icy snow conditions (OR=24.33) or while skiing during snowfall (OR=16.63).²¹

Two studies identified the type of playing surface as a risk factor for injury. In 2002, Pope et al.²² found that rubber matting on a military obstacle course was correlated with the number of ACL injuries sustained in the Australian army ($\chi^2=4.76$).²² Orchard et al.²⁰ found that in Australian football, individuals participating on fields with Bermuda grass are at an increased risk (RR=1.87).²⁰ Other risk factors included: the use of traditional skis (versus carving skis) for recreational female skiers (OR=10.49),²¹ increased sport participation sessions per week (adolescents; < 3 days per week female and male Hazard Ratio=2.0; > 4 days per week, female, male Hazard Ratio= 8.5, 4.0),²³ and individuals who participated in collegiate sports were at an increased risk of injury compared to high school sport participants (RR=2.38).²⁴

The identified weather-related and playing surface factors are out of an individual's control, however, some of these factors (i.e. playing surface) may be modified by the overseeing organizations. The risk factor of participation level may be modified by an individual (i.e. self-regulating participation), though typically this along with sport level may be predetermined and interlinked factors. The type of ski use in recreational skier is modifiable and reliant on individual choice.

Intrinsic Risk Factors

There were a total of 37 risk intrinsic factors identified in the review of literature. The risk factors were further subdivided in to 17 anatomic, eight neuromuscular, six physiologic, three biomechanical, and one genetic. The final two risk identified factors did not align with prior categorizations (Table 3).

Anatomic Factors

In multiple studies it has been reported that individuals who sustain ACL injury have intercondylar notch stenosis or a narrow intercondylar notch as determined by notch width index.²⁵⁻²⁹ Furthermore, for each millimeter decrease in the

Table 2. Assessment of risk of bias.

Author	A	B	C	D	E	F	G	H	I	J	K	L	M	No	Score
Alentorn-Geli 2015 ⁵³	No	No	Yes	U	No	No	U	No	U	U	U	U	U	Yes	2
Beynnon 2006 ⁶⁰	No	No	Yes	No	No	No	Yes	U	U	U	No	U	NA	Yes	3
Beynnon 2014a ³⁵	No	U	U	No	U	U	Yes	Yes	U	U	No	U	U	Yes	3
Beynnon 2014b ⁴²	No	No	Yes	U	No	U	U	Yes	U	U	Yes	Yes	U	No	4
Beynnon 2014c ²⁴	No	No	U	No	No	No	U	Yes	No	U	No	U	NA	U	1
Bisson 2010 ³⁴	No	U	U	No	U	U	Yes	Yes	U	U	U	U	U	Yes	3
Chaudhari 2009 ⁴⁸	No	U	Yes	U	U	U	U	Yes	U	NA	No	NA	NA	Yes	3
Dare 2015 ⁴¹	No	U	U	Yes	U	U	U	Yes	U	U	No	U	No	Yes	3
Everhart 2010 ²⁹	No	No	Yes	No	U	Yes	Yes	Yes	No	U	No	U	NA	U	4
Fernández-Jaén 2015 ²⁸	No	No	Yes	U	No	No	U	No	U	U	No	U	NA	Yes	2
Flynn 2005 ⁷¹	No	No	U	U	No	No	No	No	No	U	No	U	NA	No	0
Häggglund 2016 ⁵⁹	Yes	U	U	U	U	U	No	Yes	No	U	No	U	NA	Yes	3
Hewett 2005 ⁵⁵	Yes	U	Yes	U	U	U	U	No	U	U	No	U	U	Yes	3
Khayambashi 2016 ⁵¹	Yes	U	No	U	U	U	Yes	Yes	U	U	Yes	Yes	U	No	5
Khoschnau 2008 ⁶³	No	No	U	U	U	No	U	No	U	U	No	U	NA	Yes	1
Kramer 2007 ⁴⁵	Yes	No	Yes	No	Yes	Yes	No	No	No	NA	NA	Yes	NA	Yes	6
LaPrade 1994 ²⁶	Yes	U	U	No	U	U	U	No	U	U	No	U	U	Yes	2
Lefevre 2013 ⁶¹	No	U	No	U	U	U	U	U	No	U	No	U	U	No	0
Lund-Hanssen 1994 ³¹	No	U	U	U	U	U	U	No	U	U	No	U	NA	Yes	1
Mannion 2014 ⁶⁹	No	U	U	U	U	U	U	Yes	No	U	No	U	U	Yes	2
Myer 2009 ⁵²	Yes	U	Yes	No	U	U	U	Yes	U	U	No	U	NA	U	3
Myer 2015 ⁵⁷	Yes	U	No	U	U	U	U	No	U	U	No	U	NA	U	1
Nilstad 2014 ⁶⁹	Yes	No	No	U	U	U	No	Yes	No	U	No	U	NA	No	2
O'Connell 2015 ⁶⁷	No	U	U	U	U	U	U	No	U	U	No	U	U	Yes	1
Orchard 1999 ¹⁹	U	No	U	U	U	U	U	No	No	U	No	U	NA	U	0
Orchard 2005 ²⁰	No	No	U	U	U	U	U	Yes	No	U	No	U	NA	U	1
Parkkari 2008 ²³	Yes	U	NA	NA	U	U	Yes	No	No	Yes	No	U	NA	U	3
Pope 2002 ²²	Yes	U	U	U	No	U	U	No	U	NA	No	U	U	Yes	2
Posthumus 2009a ⁶⁵	No	U	No	No	U	U	U	No	No	NA	No	NA	NA	Yes	1
Posthumus 2010 ⁶⁶	No	No	Yes	No	No	No	No	No	U	U	No	U	NA	Yes	2
Posthumus 2009b ⁶⁴	No	No	Yes	U	No	No	No	Yes	U	U	No	U	NA	U	2
Posthumus 2012 ⁶⁸	No	No	Yes	No	No	No	No	Yes	U	U	No	U	NA	Yes	3
Quatman 2011 ⁵⁶	Yes	U	U	U	No	No	U	No	U	NA	No	NA	NA	Yes	2
Raschner 2012 ⁴⁹	No	U	U	No	U	U	No	U	U	U	No	U	NA	U	0
Ruedl 2009 ⁶²	No	U	Yes	U	U	U	No	Yes	U	U	No	U	U	No	2
Ruedl 2011 ²¹	No	No	No	U	U	U	U	No	No	U	No	U	U	Yes	1
Ruedl 2012 ⁷²	No	No	No	No	No	No	U	Yes	No	NA	NA	NA	NA	Yes	2
Saper 2016 ⁴⁴	No	U	U	No	U	U	U	Yes	No	U	No	NA	NA	Yes	2
Shaw 2015 ³³	No	U	U	U	U	U	U	Yes	U	U	No	U	NA	Yes	2
Simon 2010 ³²	No	U	U	U	U	U	U	Yes	U	NA	No	NA	NA	Yes	2
Souryal 1993 ²⁵	Yes	No	U	NA	U	Yes	Yes	Yes	No	U	No	Yes	Yes	No	6
Stijak 2014 ⁴⁶	No	No	U	U	U	U	U	Yes	U	U	No	U	NA	Yes	2
Sturnick 2014a ³⁶	U	U	U	U	U	U	Yes	Yes	U	NA	No	NA	NA	U	2
Sturnick 2014b ³⁷	Yes	U	U	U	U	U	U	Yes	U	U	No	U	NA	Yes	3
Sturnick 2015 ³⁰	No	U	U	U	No	No	U	No	U	U	No	U	U	Yes	1
Tainaka 2014 ⁵⁸	No	No	Yes	U	Yes	U	U	Yes	U	U	No	U	NA	U	3
Terauchi 2011 ³⁹	No	No	U	U	No	No	U	Yes	U	U	No	U	NA	Yes	2
Todd 2010 ⁴⁰	No	No	U	NA	U	No	Yes	Yes	No	U	NA	Yes	NA	U	3
Uhorchak 2003 ¹²	Yes	No	U	No	Yes	Yes	Yes	Yes	No	U	Yes	Yes	Yes	No	8
Vyas 2011 ⁴³	No	No	No	U	U	U	U	No	U	U	No	U	NA	Yes	1
Whitney 2014 ⁴⁷	No	No	U	No	No	No	U	Yes	U	U	No	U	NA	U	1
Xiao 2016 ²⁷	No	U	Yes	U	U	U	Yes	No	No	U	No	U	NA	Yes	3
Zazulak 2007 ⁵⁰	Yes	No	Yes	U	Yes	Yes	Yes	No	No	U	No	U	Yes	U	6
Zebis 2009 ⁵⁴	Yes	No	U	No	U	U	Yes	No	U	U	No	U	No	Yes	3
Zeng 2014 ³⁸	No	U	Yes	U	Yes	Yes	Yes	Yes	U	U	No	U	NA	Yes	6

Column Abbreviations: A=Prospective study; B=Concealed/blind group assignment; C=Group similarities at baseline; D=participant blinding; E=data collector blinding; F=outcome assessor blinding; G=previous knee injuries excluded; H=results specified for non-contact; I=no influence of other risk factors; J=acceptable compliance; K=dropout reasons reported; L=acceptable dropout rate; M=duration of intervention comparable; N=intention to treat analysis.

Yes= criteria was explained and acceptable (1 point); No= criteria missing or not acceptable (0 points); U= Unknown, criteria not explained or unclear; NA = not applicable (0 points).

Table 3. Summary of risk factors.

Category	Risk Factor ^a	Sex	N	Quality ^b	Studies	Risk assessment	95% CI
Extrinsic							
Weather conditions	During snowfall (skiing)	F	1	1 (0)	Ruedl 2011 ²¹	OR ^c : 16.63	1.8-152.1
	Icy conditions (skiing)	F	1	1 (0)	Ruedl 2011 ²¹	OR ^c : 24.33	6.8-86.5
	High 28 day evaporation rate	M	1	0 (0)	Orchard 1999 ¹⁹	RR ^d : 2.8	1.53-5.10
	No rainfall during match (wet ground)	M	1	1 (0)	Orchard 2005 ²⁰	RR ^d : 1.55	0.46-5.19
	Low previous year rainfall	M	2	0.5 (0-1)	Orchard 1999 ¹⁹ Orchard 2005 ²⁰	RR ^d : 1.93 RR ^d : 1.5	1.13-3.34 0.97-2.32
Playing surface	Rubber matting (military obstacle course)	B	1	2 (0)	Pope 2002 ²²	-	-
	Bermuda Grass	M	1	1 (0)	Orchard 2005 ²⁰	RR ^d : 1.87	1.26-2.77
Sport level	College level (compared to high school)	B	1	1 (0)	Beynnon 2014c ²⁴	RR ^d : 2.38	1.55-3.54
Ski Type	Traditional skis	F	1	1 (0)	Ruedl 2011 ²¹	OR ^c : 10.49	2.0-54.5
Sport participation	Greater weekly sport participation (\geq 4 time/week)	B	1	3 (0)	Parkari 2008 ²³	HR ^e : Female: 8.5 HR ^e : Male: 4.0	4.3-16.4 2.7-6.1
Intrinsic							
Anatomic	Non-dominant leg injury	F	2	2.5 (2-3)	Häggglund 2016 ⁵⁶ Ruedl 2012 ⁷³	- OR ^c : 2.0	- 1.0-3.8
	Generalized joint laxity	B	2	7 (6-8)	Uhorchak 2003 ¹² Kramer 2007 ⁴⁵	RR ^d : 2.8 -	- -
	Genu Recurvatum	F	1	6 (0)	Kramer 2007 ⁴⁵	-	-
	Decreased ACL width	B	1	2 (0)	Stijak 2014 ⁴⁶	-	-
	Increased ACL length	B	1	2 (0)	Stijak 2014 ⁴⁶	-	-
	ACL volume (decreased)	B	2	1.5 (1-3)	Chaudhari 2009 ⁴⁸ Whitney 2014 ⁴⁷	- OR ^c : 0.817	- 0.72-0.93
	Decreased notch width or notch width index	B	11	2.9 (1-8)	Everhart 2010 ²⁹ Fernández-Jaén 2015 ²⁸ LaPrade 1994 ²⁶ Lund-Hanssen 1994 ³¹ Shaw 2015 ³³ Simon 2010 ³² Souryal 1993 ²⁵ Sturnick 2015 ³⁰ Uhorchak 2003 ¹² Whitney 2014 ⁴⁷ Xiao 2016 ²⁷	- OR ^c : 0.87 OR ^c : 66.0 OR ^c : 7.0 - - - OR ^c : 1.5 RR ^d : 3.8 OR ^c : 0.70 -	- 0.82-0.92 20-218 2-24 - - - - - 0.57-0.85 -
	Greater alpha angle	B	1	2 (0)	Fernández-Jaén 2015 ²⁸	OR ^c : 1.049	1.01-1.08
	Increased tibial tuberosity to trochlear groove distance	B	1	2 (0)	Saper 2016 ⁴⁴	-	-
	Increased medial tibial plateau depth	B	3	4 (2-3)	Beynnon 2014a ³⁵ Beynnon 2014b ⁴² Bisson 2010 ³⁴	- OR ^c : 1.15 -	- 1.04-1.27 -
	Increased lateral tibial plateau depth	M	1	3 (0)	Bisson 2010 ³⁴	-	-
Anatomic	Increased lateral or posterior tibial plateau slope	B	9	2.8 (1-6)	Beynnon 2014a ³⁵ Bisson 2010 ³⁴ Dare 2015 ⁴¹ Simon 2010 ³² Sturnick 2014b ³⁷ Sturnick 2015 ³⁰ Terauchi 2011 ³⁹ Todd 2010 ⁴⁰ Zeng 2014 ³⁸	- - - - OR ^c : Female: 1.155 OR ^c : 1.324 - - -	- - - - 1.07-1.25 1.14-1.55 - - -
	Increased femoral plateau angle	F	1	2 (0)	Terauchi 2011 ³⁹	-	-
	Increased medial tibial slope (open physis)	B	1	1 (0)	Vyas 2011 ⁴³	-	-
Conflicting Evidence	Decreased medial tibial spine width/volume	B	2	5 (2-8)	Sturnick 2014a ³⁶ Uhorchak 2003 ¹²	OR ^c : Male: 1.5 -	- -
	Increased thickness of intercondylar notch bony ridge	B	2	2.5 (1-4)	Everhart 2010 ²⁹ Whitney 2014 ⁴⁷	- OR ^c : 1.273	- 0.97-1.67
	Lateral middle cartilage slope	B	2	1.5 (1-3)	Sturnick 2014b ³⁷ Sturnick 2015 ³⁰	- Multiple	- -
Neuromuscular	Decreased resistance to fatigue	M	1	2 (0)	Alentorn-Geli 2015 ⁵⁴	-	-
	Altered EMG muscular pre-activity	F	1	3 (0)	Zebis 2009 ⁵⁵	-	-
	Core stability	F	1	6 (0)	Zazulak 2007 ⁵¹	Multiple	-
	Decreased knee abductor strength	B	1	5 (0)	Khayambashi 2016 ⁵²	OR ^c : 1.12	1.05-1.20
	Decreased hip external rotation strength	B	1	5 (0)	Khayambashi 2016 ⁵²	OR ^c : 1.23	1.08-1.39
	Decreased hamstring strength	F	1	3 (0)	Myer 2009 ⁵²	-	-
	Multi-Factor strength	B	1	0 (0)	Raschner 2012 ⁵⁰	Multiple	-
Biomechanical	Iliotibial band flexibility	F	1	6 (0)	Kramer 2007 ⁴⁵	-	-
	Increased knee abduction moment and angle on landing	F	2	2 (1-3)	Hewett 2005 ⁶⁰ Myer 2015 ⁵⁷	- -	- -
	Increased knee valgus on landing	F	2	2.5 (2-3)	Hewett 2005 ⁶⁰ Quatman 2011 ⁶¹	- Multiple	- -
	Decreased hip external (ER) & internal (IR) rotation	B	1	3 (0)	Tainaka 2014 ⁶³	OR ^c : IR: 0.18 OR ^c : ER: 0.23	0.10-0.34 0.14-0.39

Table 3. Summary of risk factors. (continued)

Category	Risk Factor ^a	Sex	N	Quality ^b	Studies	Risk assessment	95% CI
Physiologic	Increased BMI	F	2	5.5 (3-8)	Uhorchak 2003 ¹² Hägglund 2016 ⁵⁹	RR ^d : 2.0 OR ^c : 2.4	- 0.96-6.0
	Increased body weight	F	1	8 (0)	Uhorchak 2003 ¹²	RR ^d : 1.9	-
	Menstrual pre-ovulatory phase	F	3	2 (2-3)	Beynon 2006 ⁵⁷ Lefevre 2013 ⁶¹ Ruedl 2009 ⁵⁹ Ruedl 2011 ²¹	OR ^c : 3.22 - OR ^c : 2.59 OR ^c : 1.88	1.09-9.52 - 1.2-5.5 0.92-3.88
	Onset of Menarche	F	1	3 (0)	Hägglund 2016 ⁵⁶	OR ^c : 6.68	0.90-49.83
	Sex	B	2	1.5 (1-2)	Beynon 2014 ^{c24} Fernández-Jaén 2015 ²⁸	RR ^d : Female: 2.10 OR ^c : Male: 2.22	1.34-3.27 1.47-3.33
	Age (>14)	B	1	3 (0)	Hägglund 2016 ⁵⁶	OR ^c : 4.59	1.77-11.9
Genetic	Genetic Factor(s) (e.g. COL1A1 polymorphism, COL3A1 AA genotype, GG genotype of DCN rs516115, etc.)	B	6	1.5 (1-3)	Khoschnau 2008 ⁶⁴ Mannion 2014 ⁶⁹ O'Connell 2015 ⁶⁸ Posthumus 2009a ⁶⁶ Posthumus 2009b ⁶⁵ Posthumus 2010 ⁶⁷ Posthumus 2012 ⁶⁹	OR ^c : 0.15 Multiple - OR ^c : 0.031 OR ^c : 6.6 OR ^c : 2.4 -	0.0-0.68 - - <0.01-1.46 1.5-29.7 1.0-5.5 -
Other	Prior ACL injury	F	1	2 (0)	Nilstad 2014 ⁷¹	OR ^c : 9.08	1.90-43.44
	Ankle Sprain History	F	1	6 (0)	Kramer 2007 ⁴⁵	-	-
	Familial predisposition (history)	F	2	1.5 (0-3)	Flynn 2005 ⁷² Hägglund 2016 ⁵⁶	- OR ^c : 3.57	- 1.0-2.97

F= female, M= male, B= both female & male, ACL= anterior cruciate ligament, N= number of studies, BMI= body mass index, EMG= electromyography

^a Risk for ACL injury if factor present; ^b From assessment of risk of bias (Table 2), presented as Median (range); ^c Odds ratio; ^d Relative risk; ^e Hazard ratio

anterior intercondylar notch width females were at an increased risk (OR=1.5) compared to males.³⁰ This risk factor has been reported in various populations, such as female handball players with a narrow intercondylar notch (OR=7.0).³¹ In both female and male army cadets, a narrow notch width (determined by notch width index one standard deviation below the mean) (OR=3.8) increases the risk of ACL injury.¹² One study demonstrated that individuals with a narrow intercondylar notch inlet (where ACL enters intercondylar notch posteriorly) was smaller for ACL injured individuals, and this measurement alone demonstrated a positive predictive value of 70%.³² Additionally, in the pediatric population individuals who sustained ACL injury have a significantly smaller notch width index when compared to their uninjured peers.³³

An increased posterior or lateral tibial slope was identified in nine studies as more prevalent in individuals with an ACL deficient knee when compared to uninjured peers.^{32,34-41} Two studies presented conflicting data with ACL injured individuals having either an increased (OR=1.324)³⁰ or decreased (OR=1.155)³⁷ lateral compartment middle cartilage slope. Additionally, one study specified that females with an increased lateral slope are 1.2 times as likely to sustain injury.⁴² Individuals who had an open lower

extremity physis were categorized into the pediatric population, and in those individuals with an open physis an increased medial tibial slope has been identified as an additional risk factor.⁴³ One study identified an increased femoral plateau angle (defined as the angle between a line tangent to the anterior femoral cortex and a line extended from the peaks of the medial tibial plateau) to be present in those female individuals who have suffered ACL injury.³⁹ Increases of an individual's alpha angle (measured from sagittal view films, intercondylar notch roof by the long axis of femur),²⁸ distance between their tibial tuberosity and trochlear groove,⁴⁴ depth of the medial tibial plateau,³³⁻³⁵ depth of the lateral tibial plateau,³⁴ and a generalized joint laxity may predispose athletes for injury to the ACL.^{12,45} The presence of genu recurvatum is related to a history of ACL injury, and may be a secondary factor in generalized joint laxity.⁴⁵ Characteristics related directly to the ligament, a decreased width,⁴⁶ decreased volume (size of ligament),^{47,48} and an increased length were reported to be predisposing factors for injury.⁴⁶ There is also conflicting evidence regarding the bony ridge within the intercondylar notch as a risk factor. Two studies reported that a decreased medial tibial spine width or volume (OR=1.5 for each 100mm decrease) placed individuals at increased likelihood of injury,^{12,36} while two other studies found an

increased thickness of the bony ridge in the intercondylar notch (OR = 1.614) to increase likelihood of injury.^{29,47} It may be generally agreed that risk factors related to an individual's anatomical structure are non-modifiable.⁴⁹

Neuromuscular Factors

Raschner et al.⁵⁰ reported that a multi-factor analysis of measures of muscular strength may be critical for prevention of injury in both male and female youth ski racers.⁵⁰ Furthermore, Zazulak et al.⁵¹ demonstrated that the ability to control core and trunk motion in reaction to perturbations in collegiate female athletes may predict injury.⁵¹ Other studies identified that strength deficits of the hip abductors and external rotators relative to body weight were predisposing individuals for injury (OR = 1.12).⁵² Specifically in female athletes, decreased hamstring strength is a predisposing factor for injury, when compared to healthy matched control males.⁵³ The use of tensiomyography (TMG) (measurement of contractile properties of muscle) in male soccer players revealed a decreased resistance to fatigue of the hamstrings group,⁵⁴ and the potential for imbalance between the hamstrings and quadriceps muscle groups may place individuals at an increased risk for ACL injury.⁵⁴ Furthermore, elite female handball and soccer athletes may be at a higher risk if electromyography muscular pre-activity of their lateral hamstrings are decreased relative to the lateral quadriceps.⁵⁵ Kramer, Denegar, Buckley, and Hertel revealed that decreased iliotibial band flexibility is related to a history of ACL injury,⁴⁵ and may be related to altered lower extremity movement placing an individual at risk.

Physiologic Factors

A higher than average weight (RR = 1.9)¹² or BMI (BMI > 19.9 kg/m², RR = 2.0; OR = 2.4)^{12,56} have been reported to place individuals at a higher risk for injury. Furthermore, individuals post menarche (after the onset of menses; OR = 6.68)⁵⁶ or present in the pre-ovulatory menstrual phase (OR = 2.59 to 3.22) are at increased risk.^{21,57-59} Sex has been identified as a risk factor, though with conflicting evidence.^{24,28} Fernandez-Jaen et al.²⁸ revealed, ACL tears (mechanism unreported) occur more frequently in males (OR = 2.217; at least 18 years old; adjusted for age), while Beynnon et al.²⁴ found, females are at

a greater risk for first-time non-contact ACL injury (RR = 2.1; adjusting for sport and level of play). Finally, individuals who are younger than 14 years are at an increased risk for injury to their ACL.⁵⁶

Biomechanical Factors

Individuals who present with the following biomechanical characteristics have been demonstrated to be at altered risk for ACL injury. Knee valgus on landing results in increased ground reaction forces,⁶⁰ placing females at an increased risk of injury.^{61,62} Furthermore, Quatman et al. reported that relative to normal landing,⁶¹ various combinations of tibial movement (e.g. anterior translation + abduction, anterior translation + external rotation, etc.) resulted in an increased strain on the ACL, with combined abduction and anterior tibial translation showing the greatest tension on the ACL (4.6 times normal).⁶¹ Moreover, Tainaka et al.⁶³ demonstrated that individuals with an increased amount of hip internal and external rotation during active range of motion relative to body weight are less likely to sustain injury compared to others (ER OR = 0.23; IR OR = 0.18).⁶³

Genetic Factors

Seven studies investigated a potential genetic predisposition for ACL injury. Five identified that the presence of variants of collagen genes (e.g. COL1A1, COL12A1) in both sexes increase the likelihood of injury to the ACL (OR = 0.8 to 6.6).⁶⁴⁻⁶⁸ One study demonstrated that matrix metalloproteinase genes, which play an important role in tissue remodeling, may have an association with injury.⁶⁹ Finally, one reported the presence or absence of polymorphisms of proteoglycan genes may predispose individuals for ACL injury (OR = 0.33 to 9.231).⁷⁰

Other Factors

The following did not fit within other categories, and were reported as risk factors in the female sex. Individuals with previous ACL injury are at a higher likelihood for injury in the same knee (OR = 9.08),⁷¹ and individuals with family history of ACL injury (immediate family) are at an increased likelihood of injury (OR = 3.57).^{56,72} When examining female youth soccer players, there was a higher prevalence of ACL injuries in their non-dominant leg.⁵⁶ Furthermore,

female recreational skiers were demonstrated to be at an increased risk of injuring their non-dominant leg compared to their dominant (OR = 2.0).⁷³

DISCUSSION

This systematic review presents a wide view of potential risk factors for ACL injury, which are both intrinsic and extrinsic in nature. The majority of the extrinsic factors identified are related to the effect weather conditions have on participants during specific sport participation or the conditions of the playing surface, which have been reported in prior reviews.¹⁵ Findings presented in this review demonstrate that both sexes may be affected by eroding conditions due to the weather and other external factors. Weather conditions related to an increase in odds of injury for women were those during recreational skiing (icy conditions and during snowfall),²¹ while the weather conditions for men were related to dry conditions on the pitch for Australian Football.^{19,20} These findings are presented by sex due to the lack of studies examining these conditions across sexes. Regarding the results of this review, the conditions of ski slopes and the rainfall for field-based participation should be considered.¹⁹⁻²¹

While there is an abundance of literature identifying intrinsic risk factors, unfortunately the majority of studies included in this review surrounded non-modifiable anatomic factors. Eleven studies reported a decreased intercondylar notch width or notch width index,^{12,25-33,47} and 11 others identified an increased lateral or posterior tibial plateau slope as a risk factor.^{30,32,34-41,43} Alentorn-Geli et al.¹⁵ reported both factors, and although they are non-modifiable, suggested that injury risk may be mitigated through the implementation of neuromuscular preventative training programs. Within anatomic risk factors, the studies reviewed have presented conflicting evidence regarding how changes in the morphometric characteristics of the bony ridge (increases/decreases in size) within the intercondylar notch affect an individual's risk of sustaining ACL injury. Future inquiry is necessary to determine whether the characteristics of this ridge are consequential.

The majority of the neuromuscular and biomechanical risk factors are presented as modifiable. Those that stand out in this review are impairments of core

stability,^{50,51} increased knee valgus, and increased knee abduction moment and angle on landing.⁶⁰⁻⁶² These risk factors may be addressed through neuromuscular preventative training programs.^{6,15} Decreased resistance to fatigue was a risk factor found only in males. Neuromuscular (e.g. EMG muscular pre-activity) and biomechanical (e.g. increased knee valgus on landing) factors were found predominantly in females. Decreases in strength and range of motion were risk factors present in both sexes. Myer et al. discuss that hamstring strength and hamstring to quadriceps ratio remain relatively unchanged as females mature, which may increase the likelihood of developing neuromuscular imbalances, thus potentially increasing females risk of sustaining ACL injury.⁵³

Some physiologic factors seem to be on the non-modifiable end of the spectrum, such as the pre-ovulatory phase of the menstrual cycle,^{21,57,58} and the onset of menarche.⁵⁶ These are viewed as non-modifiable as the individual may not have control over if or when they happen. The final risk factor that showed a high prevalence in the literature review is the potential for a genetic predisposition. There were six separate studies that demonstrated that variants of multiple collagen genes may play a role in the development of future ACL injury in both sexes.⁶⁴⁻⁶⁹ Similar to physiologic factors, an individual does not have control over their genetic makeup. However, the individual may take themselves out of participation in order to circumvent the potentially negative affect of some of these factors

Along with national sports governing bodies (i.e. NCAA, National Federation of State High School Association [NFHS]), colleges/universities and high schools play a crucial role in contributing to safety during sport participation by governing their affiliated teams and through the development of their sports venues. When adjusted for socioeconomic, health, and lifestyle variables, adolescents who participate in organized sport activities at any level more than four times per week are at higher odds of injury (female, male; Hazard Ratio = 8.5, 4.0).²³ This places sport governing bodies in a key role for implementation of preventative strategies focusing on the amount of time per week individuals participate. Managing participation by maintaining adequate

recovery time may be a strategy for the reduction of this risk factor, as neuromuscular fatigue may lead to a negative change in mechanics (e.g. increased valgus collapse) during landing tasks.^{74,75} On the development and maintenance of sporting venues, the type of grass used on fields has been shown to play a role in risk of ACL injury, specifically for men with Bermuda grass increasing their risk.²⁰ Furthermore, for those institutions which house ski teams, the maintenance of the slopes may play a role for their conditions.²¹ Future research regarding eroding weather conditions and playing surface type should focus on the effects applicable to both sexes in order for more informed decisions to be made by sport governing bodies (i.e. NCAA, NFHS) and universities or high schools for decisions on cancellation of sport activities based on weather and for the development and refurbishing of sporting venues.

Limitations to this systematic review include that this report did not include a synthesis of previous systematic review findings, though attempts to encompass risk for both sexes were made. High risk of bias for included studies is a limitation, however, Table 2 provides clarification as to where the bias in each study may come from. Another limitation includes the search of only two databases for articles. Future directions for research regarding ACL injury include a clarification of conflicting evidence of risk factors and identification of specific methods for alteration of known factors.

CONCLUSION

This systematic review attempts to describe documented risk factors for ACL injury for both sexes to further preventative efforts. While there were a few male specific risk factors, and a number found in both sexes, most of the risk factors identified were present for females. The information presented herein reaffirms that injury to the ACL likely results from a plethora of underlying risk factors. While some of the factors presented in this review may be modified, there are many which an individual may not be able to control or modify. The majority of extrinsic risk factors fall in the non-modifiable category. The nature of sport itself will continue to put those who choose to participate at some level of risk to injury. It may prove beneficial to attempt to

change those factors with potential for modification (i.e. field type) as those may provide a widespread reduction of exposure. Further research on modifiable factors may provide insight for the development and advancement of injury prevention programs with the aim to decrease the incidence of injury.

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