Sexual Dimorphisms in Anterior Cruciate Ligament Injury

A Current Concepts Review

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Background: Although most anterior cruciate ligament (ACL) injuries occur in male athletes, female athletes are consistently observed to be at a higher risk for sports-specific ACL injury.

Purpose: To provide a thorough review of what is known about the sexual dimorphisms in ACL injury to guide treatment and prevention strategies and future research.

Study Design: Narrative review.

Methods: We conducted a comprehensive literature search for ACL-related studies published between January 1982 and September 2017 to identify pertinent studies regarding ACL injury epidemiology, prevention strategies, treatment outcomes, and dimorphisms. By performing a broad ACL injury search, we initially identified 11,453 articles. After applying additional qualifiers, we retained articles if they were published in English after 1980 and focused on sex-specific differences in any of 8 different topics: sex-specific reporting, difference in sports, selective training, hormonal effects, genetics, neuromuscular and kinematic control, anatomic differences, and outcomes.

Results: A total of 122 articles met the inclusion criteria. In sum, the literature review indicated that female athletes are at significantly higher risk for ACL injuries than are their male counterparts, but the exact reasons for this were not clear. Initial studies focused on intrinsic differences between the sexes, whereas recent studies have shifted to focus on extrinsic factors to explain the increased risk. It is likely both intrinsic and extrinsic factors contribute to this increased risk, but further study is needed. In addition to female patients having an increased risk for ACL injuries, they are less likely than are male patients to undergo reconstructive surgery, and they experience worse postsurgical outcomes. Despite this, reconstructive surgery remains the gold standard when knee stability, return to sports, and high functional outcome scores are the goal, but further research is needed to determine why there is disparity in surgical rates and what surgical techniques optimize postsurgical outcomes for female patients.

Conclusion: Male athletes often predominated the research concerning ACL injury and treatment, and although sex-specific reporting is progressing, it has historically been deficient. ACL injuries, prevention techniques, and ACL reconstruction require further research to maximize the health potential of at-risk female athletes.

Keywords: knee; ACL; female athlete; medical aspects of sports; anatomy; epidemiology

Approximately 120,000 anterior cruciate ligament (ACL) injuries occur annually, with a peak incidence in the adolescent to young adult years.³⁸ While male athletes account for most injuries in the general population (because of their greater exposure to athletic tasks predisposing them to ACL injury), female athletes are consistently observed to be at higher risk for sports-specific injury.³⁶ While the reported ratios of female-to-male ACL injury range from from 2:1 to as high as 9:1, variability exists by sex and sport, as well as response to mitigation via injury reduction training programs.^{39,87} The exact reasons for this discrepancy are not fully known.

Figure 1 stratifies the studies included in this review by topic. Early studies focused heavily on hormonal, anatomic, and genetic difference but these studies did not definitively account for the discrepancy. As such, most recent studies have shifted to focus on kinematics and sport-specific training, which also have not fully accounted for the discrepancy. We hypothesized that any disparity in the incidence of ACL injuries between male and female athletes was multifactorial, resulting from both intrinsic (biochemical, hormonal, neuromuscular, kinematic, and anatomic differences) and extrinsic factors (differing sports and a selective training bias). The

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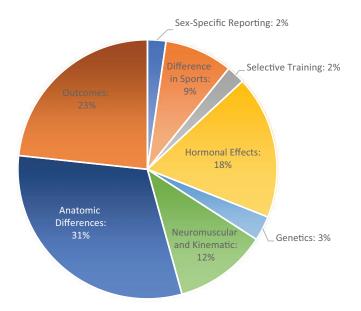


Figure 1. Stratification of studies on sexual dimorphisms in anterior cruciate ligament injury by focus of differences.

consequences of ACL injury can be physically, psychologically, and financially significant—both in the short and the long terms.^{44,104} The average cost of an ACL injury ranges from \$17,000 to \$25,000.²⁵ Further, such injuries frequently result in loss of athletic scholarships, loss of competitive season or career, and decreased productivity in the short term and posttraumatic osteoarthritis in the long term.¹⁰⁴

Although the rates of ACL reconstruction (ACLR) have been increasing for women, with a peak age of reconstruction at 17 years, outcomes vary by sex.^{29,70} Thus, thorough understanding of what is currently known about the differences in ACL injury predilection and mechanisms, prevention strategies, and outcomes of current treatment options between female and male patients is essential to guide treatment and prevention strategies. The purpose of this study was to provide a thorough review of what is known in these areas in order to guide future research.

METHODS

With the assistance of the US Army Medical Department Center and School medical librarians, we conducted a comprehensive literature search to identify pertinent studies published between January 1982 and September 2017 regarding ACL injury epidemiology, prevention strategies, treatment outcomes, and dimorphisms. From this broad search 11,453 articles were initially identified. Emphasis was placed on recent and higher-level studies with keywords anterior cruciate ligament, sex based, sex differences, gender based, gender differences, and dimorphisms. After applying these qualifiers, articles were retained if they were published in English after 1980. From this extensive literature search, 122 manuscripts were selected.

RESULTS

Sex-Specific Reporting

Female participation in athletics has increased dramatically since the institution of Title IX of the Education Amendments Act of 1972. Between 1982-1983 and 1997-1998, National Collegiate Athletic Association female participation increased by 69%, whereas male participation increased by 3%.⁷⁷ As the number of women in sports has increased, so has their incidence of ACL injuries.¹⁰⁴ Although female athletes are reportedly more likely to sustain ACL injuries, the exact difference in incidence among female athletes versus male athletes is not known, as incidence reporting is often not sex specific. Sutton and Bullock¹⁰⁴ reported 100,000 to 250,000 ACL tears per year in the United States but did not separate incidence by sex. A systematic review, including a multicountry analysis, reported the annual incidence of ACL tears among the general population, amateur athletes, and high-level athletes as 0.05%, 0.03% to 1.62%, and 0.15% to 3.7%, respectively, but did not discuss sex-based differences in depth.⁷⁷ In 2012, Moses et al,⁷⁷ focusing on sex-specific reporting in the literature, asserted male bias exists in research and expressed the importance of its recognition. For example, animal studies predominantly use male participants. In addition, girls and women comprise <40% of participants in clinical trials. For decades, researchers have ignored sex as an affecting variable or have deliberately excluded females to avoid confounders of gestational status and/or the menstrual cycle.⁵² To better prevent, diagnose, and treat ACL injuries, it is necessary to study and report sex differences.⁵²

Difference in Sports

ACL injury differences between female and male patients have been examined for disparities among sports. The literature has indicated the majority of ACL injuries in female

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TABLE 1 Literature Support for Sport-Specific Increase in ACL Injury Risk Ratios for Female Athletes

Study	Soccer	Basketball	Other
Arendt and Dick ⁸	2.4 imes	4.1 imes	
Gwinn et al^{40}	4 imes	4 imes	Military obstacle course: $9.74 \times$
			Rugby: $4 \times$
Lindenfeld et al ⁶⁴	3-5 imes	_	
Medvecky et al ⁷⁴	_	5-7 imes	_
Mihata et al ⁷⁶	2.3 - $2.9 \times$	3.5- $4.1 imes$	_
Mountcastle et al ⁷⁸	0.84 imes	2.4 imes	Gymnastics: $5.67 \times$
	$1.27 imes^a$	$3.0 imes^a$	Obstacle course: $3.72 \times^a$
Prodromos et al ⁸⁷	2.67 imes	3.5	Wrestling: $4.05 \times$
Stanley et al ¹⁰¹	2.8 imes	3.25 imes	—

 $^a \rm Noncontact$ injury. Dashes indicate no data reports/none reported.

athletes are noncontact (70%) versus contact injuries (30%).^{8,44,74,76,101,104} ACL injuries are of specific concern for multidirectional sports requiring cutting, jumping, and rapid speed changes such as soccer and basketball.⁷⁷ As such, most of the literature had focused on sports that require these maneuvers. The risk of an ACL injury in a female collegiate soccer or basketball player is 4.4% to 5% per year as opposed to 1.7% for men.¹⁰⁴ Table 1 summarizes the multiple studies finding female athletes to be at increased risk of ACL injury when compared with their male counterparts.

Selective Training

A selective training effect as reasoning for decreased incidence of ACL injuries in male versus female athletes has been proposed.^{37,76} This theory suggests men begin playing their chosen sport at a younger age than women do, resulting in higher proficiency and fewer ACL injuries. However, the evidence supporting this theory has major methodological flaws. Since the enactment of Title IX, female athletes have begun participating in chosen sports at increasingly earlier ages compared with male athletes. Despite this, there has not been a corresponding decrease in female ACL injury rates over the past decade.^{37,76}

Although Silvers and Mandelbaum⁹⁶ suggested selective training decreases ACL injury risk, they also suggested selective training must be optimally implemented, noting a minimum of 6 to 8 weeks is required to achieve a neuromuscular effect. A number of operationally relevant inquiries regarding use of selective training to reduce ACL injury risk remain, including the optimum timing of specific training within the sports season (eg, preseason, season, off-season); prevalence of degradation and necessity, if any, of retraining; differences for training the novice versus the experienced athlete; and whether the training effects and requirements are amenable to universal application or exhibit variation based on sex, sport, and skill level.

	Follicular Phase	Ovulatory Phase	Luteal Phase
Increased risk of ACL injury	Arendt et al ⁹ Arendt et al ¹⁰ Myklebust et al ⁸⁰ (early follicular) Slauterbeck and Hardy ⁹⁸	Wojtys et al ¹¹⁶ Wojtys et al ¹¹⁷	Myklebust et al ⁸⁰ (late luteal)
Increased ACL laxity		Park et al ⁸³	Deie et al ²⁶ Heitz et al ⁴³ Shultz et al ⁹⁵
Increased strength and fatigue, decreased relaxation	_	Sarwar et al ⁹²	_

 TABLE 2

 Literature Support for Menstrual Cycle Phase

 Effect on ACL Injury^a

 $^a\mathrm{ACL},$ anterior cruciate ligament. Dashes indicate no data reports/none reported.

Hormonal Effects

Hormones are one of the most readily apparent differences between male and female athletes. As such, much of the research on endocrine effects on the ACL has focused on cycling hormone levels during the menstrual cycle-mainly estrogen and relaxin.^{31,74,95,98,120} Estrogen receptors are present on ACL fibroblasts, which produce collagen, the main tensile strength component for the ACL.⁹⁸ It is suspected that when estrogen is abundant, collagen production decreases, resulting in decreased ACL strength.^{37,98} It has also been theorized that vasodilation effects of estrogen increase tissue water content, disrupting ligamentous stability.⁷⁴ Relaxin decreases ligamentous tensile strength via release of metalloproteases leading to collagen breakdown.³¹ Thus, these hormones may play a direct role in weakening the ACL, possibly leading to an increase in female ACL injury.^{31,37,74,98}

However, the effects of cycling levels of estrogen and relaxin on knee joint laxity, mechanics, and muscle control are not well defined. As demonstrated in Table 2, although multiple studies have indicated increased ACL injury or laxity during different phases of the menstrual cycle, there is little consensus as to which phase, if any, puts the ACL at most risk. Further, studies have often measured different outcomes, injury versus laxity, making them difficult to compare. The clinical correlation between knee laxity and its risk for ACL injury rates is unclear. Although Park et al⁸⁴ found there was a significant difference in knee laxity throughout the menstrual cycle, they reported it did not lead to clinically significant changes in knee-joint mechanics or any increased risk of ACL injury. Sarwar et al⁹² found increased quadriceps strength and fatigability with decreased relaxation during ovulation. Further, Shultz et al⁹⁵ advocated research be guided to look at the menstrual cycle phase 3 to 4 days prior to the increase in laxity as the culprit for increased laxity due to the dosedependent antagonist effect of estrogen and the 3- to 7day delay in tissue modulation.¹²⁰ Finally, other studies have found no discernable relationship between the menstrual cycle and knee laxity, stiffness, or muscle strength.^{22,54,57}

The effect of relaxin on ACL laxity and injury rates is also not yet well defined. Dragoo et al³¹ identified relaxin receptors only in female patients, leading some to believe this to be a major difference between female and male ACL injury. They found a relationship between relaxin concentration and ACL injury. Elite collegiate athletes sustaining ACL tears had significantly higher risks when their serum relaxin concentrations were increased and 4 times higher risk when concentrations reached 6.0 pg/mL. However, Arnold et al¹¹ and Wolf et al¹¹⁸ reported no relationship between joint laxity and relaxin concentration.

If the menstrual cycle increases ACL laxity, predisposing female athletes to increased risk of ACL injury, oral contraceptive pill (OCP) use should theoretically mitigate this risk. However, this too is not well defined. Although Rahr-Wagner et al,⁸⁹ in a study of >13,000 participants, found a protective association between OCP use and ACL injury, they were unable to correct for selection bias and confounding variables and were thus unable to make a definitive conclusion regarding prophylactic use of OCPs. Other studies have found protective benefits from OCP use in reducing knee and ankle injuries.^{9,14,31,57,89} However, Sarwar et al⁹² found no change in quadriceps strength, fatigability, or relaxation in patients taking OCPs, and Bell et al¹⁴ found OCPs did not affect muscle stiffness or provide protection from ACL injury. The effects of estrogen, relaxin, and prophylactic OCP use on ACL laxity, knee mechanics, and muscle strength remain poorly defined. Although it is unquestioned that hormone cycling during the menstrual cycle affects knee ligaments, especially the ACL, the heterogeneity in methodology and reported outcomes makes it difficult to discern the discrepancy in research findings. The current literature as it pertains to the menstrual cycle is insufficient for guiding prevention, risk mitigation, or treatment strategies. Clinically important future research should address multiple variables such as training intensity and frequency, competition, types of rehabilitation, and even surgery, as well as their optimization within normal phases of the menstrual cycle.

Genetics

Research into genetic risk factors for ACL injury is in the early stages of gene identification and is often not risk stratified by sex. O'Connell et al⁸¹ reported COL1A1, COL5A1, and COL12A1 are significantly overexpressed in ACL–injured athletes, but their data were reported in the aggregate without breakdown between female and male patients. Although Rahim et al⁸⁸ focused on 2 genotypes with representational differences in those with ACL injury and controls, the only sex-specific notation they mentioned was that of a kinase insert domain-receptor gene possibly playing a protective role in female patients. As research

 TABLE 3

 Literature Support for Genetic Role in the Sex-Based

 Disparity in ACL Injuries^a

Study	Gene	Effect
Johnson et al ⁵⁵	WISP2 (Wnt-1-inducible signaling-pathway protein-2)	WISP2: decreased expression in female patients with ACL injury
	FMOD (fibromodulin) ACAN (aggrecan)	<i>FMOD, ACAN</i> : increased expression in female patients with ACL injury
Posthumus et al ⁸⁶	COL5A1/COL12A1 (collagen5a1/ collagen12a1)	Increased expression in female patients with ACL injury
Rahim et al ⁸⁸	KDR (kinase insert domain receptor)	Protective in female patients against ACL injury

^aACL, anterior cruciate ligament.

regarding genetic effect on ACL injury has continued, sex-specific reporting has increased. Table 3 summarizes current genetic research supporting the hypothesis that differences in female versus male genetic makeup contribute to differing risk of ACL injury. Although it is important to discover genetic risk factors for ACL injury to identify individuals at risk, obviously genetic makeup is a nonmodifiable risk factor. In order to develop targeted therapies, genetic research should strive to identify and determine whether specific genes predispose to, or protect from, ACL injury.

Neuromuscular and Kinematic Control

Neuromuscular control and biomechanical factors are important modifiable risk factors in the dichotomy between male and female ACL injury.⁶² There are multiple hypotheses to explain this observation that include (1) estrogen possibly altering neuromuscular control with increased quadriceps strength⁹² and (2) hamstring-quadriceps imbalance possibly leading to improper dynamic knee stabilization in women.^{3,24,44,62,79} However, Bennett et al¹⁵ reported an imbalance in the hamstring-quadriceps ratio not being a significant predictor of anterior tibial shear force.

Female athletes also demonstrate greater valgus moment arms during landing and cutting maneuvers that place undue stress on the ACL.^{13,18,35,44,73,82} These valgus moments are worsened by the point of maximal height velocity.⁴⁶ Finally, Leetun et al⁶¹ reported that the lack of core and hip stabilization in young girls, specifically hip abduction weakness, is a predictor of lower extremity injury. These risk factors, however, can be modified. Orishimo et al⁸² reported female dancers not demonstrating the neuromuscular and kinematic deficits that female team sports athletes do, suggesting that early training in proper landing technique, strength, and core stabilization in prepubertal female athletes can decrease ACL injuries.^{50,61} Longitudinal study of ACL injury prevention programs is required to definitively determine the effect of

Posterior Tibial Slope		Notch Width		ACL Volume/Cross-sectional Area	
In Favor	Against	In Favor	Against	In Favor	Against
Beynnon et al ¹⁷ Beynnon et al ¹⁶ Hashemi et al ⁴² Hashemi et al ⁴¹ Lipps et al ⁶⁵ Markolf et al ⁷¹ Simon et al ⁹⁷ Sturnick et al ¹⁰³ Todd et al ¹⁰⁸	Meister et al ⁷⁵	Anderson et al ⁶ Domzalski et al ³⁰ Emerson ³² Everhart et al ³³ Hoteya et al ⁴⁷ Lund-Hanssen et al ⁶⁸ Shelbourne et al ⁹⁴ Simon et al ⁹⁷ Souryal and Freeman ⁹⁹ Sturnick et al ¹⁰³ Uhorchak et al ¹¹⁰ Van Eck et al ¹¹² Whitney et al ¹¹⁵ Wolters et al ¹²²	Anderson et al ⁵ Arendt and Dick ⁸ Brandon et al ²⁰ Chandrashekar et al ²³ Van Eck et al ¹¹¹ Hewett et al ⁴⁵ Hutchinson and Ireland ⁵¹ Ireland et al ⁵³ LaPrade and Burnett ⁵⁹ Lombardo et al ⁶⁷ Schickendantz and Weiker ⁹³ Teitz et al ¹⁰⁶	Anderson et al ⁵ Chandrashekar et al ²³ Dienst et al ²⁸ Lipps et al ⁶⁵ Stijak et al ¹⁰² Whitney et al ¹¹⁵	None

TABLE 4Literature in Favor of or Against Specific Anatomic Differences as Contributing Factorsto Sex-Based Disparity in ACL Injuries^a

^aACL, anterior cruciate ligament.

TABLE 5
Literature in Favor of Other Anatomic Variables
as Contributing Factors in the Sex-Based Disparity
in ACL Injuries ^a

Anatomic Variable	Study
Q angle Thigh length ACL tensile properties Notch size/ACL size mismatch	Zelisko et al ¹²¹ Beynnon et al ¹⁶ Chandrashekar et al, ²³ Johnson et al ⁵⁵ Chandrashekar et al, ²³ Stijak et al ¹⁰²
Femoral notch ridge size Meniscal slope	Whitney et al ¹¹⁵ Meister et al ⁷⁵

^aACL, anterior cruciate ligament.

neuromuscular control and kinematics on the incidence of ACL injury.

Anatomic Differences

The anatomic differences between female and male participants has been intensely researched without solid conclusions as to which differences, if any, increase risk of ACL injury in female participants. Tables 4 and 5 outline ACL anatomic differences between female and male participants along with the studies finding whether specific anatomic differences are increased risk factors for ACL injury. As is apparent from the tables, research has not demonstrated a clear-cut anatomic difference accounting for increased incidence of ACL injury in female patients. Further, as anatomic differences are nonmodifiable risk factors, their use may be limited in designing prevention programs. Some authors have proposed that the measurements be used as a screen to identify athletes at risk and then pursue neuromuscular and kinematic training intervention.⁴⁴

Outcomes

Sex-specific reporting in outcome measures is important in determining the appropriate surgical intervention. Mall et al⁷⁰ reported that between 1996 and 2006, the incidence of ACLR nearly doubled, with the fastest growing populations being female and patients <20 years of age. Leathers et al⁶⁰ found the overall incidence of ACLR increased in the United States by 16.9% between 2004 and 2009 and male patients underwent the procedure twice as often as female patients despite the higher incidence of female ACL injury. The reasons for this gap, which could include unconscious bias favoring surgery for male patients at the patient-physician level, are unknown and require further study.

Just as the cause of ACL injury disparity between female and male patients is not well defined, ACLR outcome measures are, likewise, not well defined. Table 6 demonstrates the considerable variability of research findings regarding ACLR outcome measures between female and male patients. Multiple authors have suggested poorer outcomes and increased rates of contralateral injury and graft rupture in female patients, opining such to be due to continued poor neuromuscular control and kinematic deficits.^{24,27,58} In contrast, Tan et al,¹⁰⁵ in a comprehensive and systematic review of 120,000 patients, found graft rupture/rerupture rates were not influenced by sex but also concluded that female patients had overall poorer outcomes, reflected in lower return-to-sports rates and lower functional outcome scores. Thompson et al¹⁰⁷ also found poor return-to-sport outcomes in female patients, whereas, Howard et al⁴⁸ found that younger college athletes with scholarship have higher

	measures ruler nem	
Contralateral ACL	Tears	
No Difference	Increased Tears in Female Patients	Increased Tears in Male Patients
Andernord et al ⁴ Brophy et al ²¹ Kaeding et al ⁵⁶ Ryan et al ⁹⁰ Thompson et al ¹⁰⁷ Webster et al ¹¹⁴	Ahldén et al ² Paterno et al ⁸⁵ Shelbourne et al ⁹⁴	None reported
	Graft Ruptures	
No Difference	Increased Ruptures in Female Patients	Increased Ruptures in Male Patients
Andernord et al ⁴ Ferrari et al ³⁴ Kaeding et al ⁵⁶ Lyman et al ⁶⁹ Ryan et al ⁹⁰ Salmon et al ⁹¹ Shelbourne et al ⁹⁴ Spindler et al ¹⁰⁰ Tan et al ¹⁰⁵	Slauterbeck and Hardy ⁹⁸	Bourke et al ¹⁹ Leys et al ⁶³ Thompson et al ¹⁰⁷ Webster and Feller ¹¹³
	Return-to-Play Rate	
No Difference	Decreased Rate in Female Patients	Decreased Rate in Male Patients
None reported	Ardern et al ⁷ Brophy et al ²¹ Tan et al ¹⁰⁵ Thompson et al ¹⁰⁷	None reported
	Functional Outcome Sco	res
No Difference	Lower Scores in Female Patients	Lower Scores in Male Patients
Ahldén et al ² Barber-Westin et al ¹² Ferrari et al ³⁴ Salmon et al ⁹¹ Spindler et al ¹⁰⁰ Tohyama et al ¹⁰⁹	Ageberg et al ¹ Tan et al ¹⁰⁵ Thompson et al ¹⁰⁷	None reported

TABLE 6 Literature on Sex-Specific Differences in Outcome Measures After ACLR^a

 $^{a}\mathrm{ACL},$ anterior cruciate ligament; ACLR, anterior cruciate ligament reconstruction.

return-to-play rates unrelated to graft type, tunnel placement and concomitant surgical procedures.

Despite female patients being reported as having worse postsurgical outcomes compared with male patients, it is agreed that ACLR is the gold standard when knee stability, return to sports, and high functional outcome scores are the goal.^{49,72} The appropriate surgical technique, graft choice, and tunnel placement and their sexspecific outcomes, however, remain elusive. Thompson et al¹⁰⁷ reported a patellar tendon graft choice in female patients leading to an acceptable decline in failure rates. However, it may lead to other complications contributing to decreased return to sports among these female athletes. More research is needed to investigate whether graft choice has a significant effect on outcomes for female versus male athletes.

CONCLUSION

Our review of the literature has shown that the ratio of female to male athletes sustaining an ACL injury ranges from 2:1 to 9:1. However, the exact reasons for this disparity have not been fully elucidated. Male patients often predominate the research concerning ACL injury and treatment, and although it is progressing, sex-specific reporting is historically deficient. It is important to understand that ACL injuries, prevention techniques, and ACLR are sex specific.

To better define the difference between women and men, sex-specific ACL tear incidence reporting must be encouraged. Further, to better delineate the sexual dimorphisms in ACL injuries to guide treatment and prevention strategies, more research and inquiry is needed as to the effect of selective training based on sex, sport, and skill level; the effects of hormones, hormone cycling and hormone modification on ACL injury; genetic risk factors for ACL injury stratified by sex; and anatomic differences between male and female patients relating to ACL injury.

Further, longitudinal investigation into the modifiable risk factors is most important to identify those at risk, modify their neuromuscular and kinematic deficits, and lower overall ACL injury rates. Improved outcomes would lead to decreased functional loss, decreased loss of scholarships, a decline in long-term osteoarthritis, and decreased cost of ACLR and rehabilitation.⁶⁶

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