# Multivariate Analysis of the Risk Factors for First-Time Noncontact ACL Injury in High School and College Athletes: A Prospective Cohort Study With a Nested, Matched Case-Control Analysis

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## Abstract:

**Background:** Multivariate analysis that identifies the combination of risk factors associated with anterior cruciate ligament (ACL) trauma is important because it provides insight into whether a variable has a direct causal effect on risk or an indirect effect that is mediated by other variables. It can also reveal risk factors that might not be evident in univariate analyses; if a variable's effect is moderated by other variables, its association with risk may be apparent only after adjustment for the other variables. Most important, multivariate analyses can identify combinations of risk factors that are more predictive of risk than individual risk factors.
**Hypothesis:** A diverse combination of risk factors predispose athletes to first-time noncontact ACL injury, and these relationships are different for male and female athletes.
**Study Design:** Case-control study; Level of evidence, 3.
**Methods:** Athletes competing in organized sports at the high school and college levels participated in this study. Data from injured subjects (109 suffering an ACL injury) and matched controls (227 subjects) from the same athletic team were analyzed with multivariate conditional logistic regression to examine the effects of combinations of variables (demographic characteristics, joint laxity, lower extremity alignment, strength, and personality traits) on the risk of suffering their first ACL injury and to construct risk models.
**Results:** For male athletes, increases in anterior-posterior displacement of the tibia relative to the femur (knee laxity), posterior knee stiffness, navicular drop, and a decrease in standing quadriceps angle were jointly predictive of suffering an ACL injury. For female athletes the combined effects of having a parent who had suffered an ACL injury and increases in anterior-posterior knee laxity and body mass index were predictive of ACL injury.

**Conclusion:** Multivariate models provided more information about ACL injury risk than individual risk factors. Both male and female risk models included increased anterior-posterior knee laxity as a predictor of ACL injury but were otherwise dissimilar.

**Keywords:** knee | anterior cruciate ligament | injury | risk factors

## Article:

Anterior cruciate ligament (ACL) disruption is common; it creates altered biomechanics about the knee; and it is frequently associated with the onset and progression of posttraumatic osteoarthritis about this joint.[2] Wide ranges of incidence rates for both ACL injury and reconstruction have been reported in the literature, but most are based on assessments performed >15 years ago.[18] While the true incidence of ACL reconstruction in the United States is unknown,[24] a recent study identified a rise in ACL reconstruction, from 86,687 (32.9 per 100,000 person-years) in 1994 to 129,836 (43.5 per 100,000 person-years) in 2006, with increased numbers of procedures occurring in females and in persons <20 years or >40 years.[23] The pathoetiology of posttraumatic osteoarthritis after ACL trauma is not completely understood; however, there is evidence that it occurs whether the injury is treated with or without surgical reconstruction.[1,22] Since there are currently no effective therapeutic options available to treat osteoarthritis in young, active individuals, many groups have developed neuromuscular training programs to reduce the risk of ACL injury. There is evidence from meta-analyses that supports the efficacy of these training programs in reducing ACL injuries; however, the effect size was small, with the number-needed-to-treat analysis demonstrating 109 athletes treated to prevent 1 ACL injury.[11,15,25] This may be attributed, at least in part, to an incomplete understanding of the factors influencing an individual's susceptibility to this debilitating injury, the fact that many concomitant injuries occur in combination with the ACL disruption, and that males and females may not all be at increased risk of suffering trauma for the same reasons.[28-30]

A systematic review of the literature on prognostic studies for ACL injury revealed that most studies have focused on potential risk factors for ACL injury in isolation.[29,30] For example, studies have found that characteristics such as the sport in which the athlete participates,[8] level of play,[8] an athlete's sex,[6,8] family history of an ACL injury,[14] increased knee laxity,[35] knee loading during landing from a jump,[17] and specific measures of geometry of the knee joint (including decreased femoral notch size, decreased ACL size, and increased posterior-inferior directed slope of the surface of the lateral tibial plateau articular cartilage) are associated with increased risk of suffering an ACL injury.[5,9,29,31,32,36]

It is likely that multiple risk factors influence the risk of injury, but only one previous study has evaluated a broad range of risk factors for ACL injury.35 Consequently, there is limited information available for the development of comprehensive, clinically applicable risk models. Such risk models are essential for the development of injury prevention programs that address the combined influence of multiple risk factors rather than focusing on one aspect of susceptibility to ACL injury. Clinically useful risk models are also needed for identifying those who are at increased risk so that they can be counseled about their chances of sustaining an ACL injury and be offered targeted interventions for injury prevention. In addition, multivariate analysis of combinations of risk factors and how they relate to injury can provide insight into whether a variable has a direct causal effect on risk or an indirect effect that is mediated by other variables. It can also reveal risk factors that might not be evident in univariate analyses; if a variable's effect is moderated by other variables, its association with risk may be apparent only after adjustment for the other variables. Most important, multivariate analyses can identify combinations of variables that are more predictive of risk than individual risk factors.

This article presents the results of multivariate analyses to assess the combined effects of variables on the risk of first-time noncontact ACL injury. The objectives were to examine how the effects of individual variables on risk are influenced by other variables and to develop multivariate risk models that could be used as screening tools to identify athletes who are at increased risk of suffering a noncontact ACL injury and might thus benefit most from preventive intervention. Separate models were derived for males and females because the univariate analyses (see the Appendix, available in the online version of this article at http://ajsm.sagepub.com/supplemental) indicate that the risk factors for noncontact ACL injury differ between the sexes.

## METHODS

This was a prospective cohort study with a nested, matched case-control analysis. The University of Vermont Committee on Human Research in the Medical Sciences Review Board approved this investigation, and each participant (and a parent or legal guardian if the participant was <18 years) provided signed informed consent before participation.

The high schools and colleges located throughout the state of Vermont were approached and invited to participate. An institution was included as a recruitment site if a licensed athletic trainer was available and he or she agreed to identify subjects who suffered a severe knee injury that was thought to involve the ACL. At the high school level, male and female athletes participated on varsity, junior varsity, and freshman teams, including lacrosse, basketball, soccer, field hockey (females only), and football (males only). At the college level, male and female athletes participated in these same sports, with the addition of rugby (males and females) and volleyball (females only). Teams from 36 institutions (28 high schools and 8 colleges) were monitored prospectively over 4 years to identify ACL injuries and recruit study participants. The athletic trainer providing medical coverage and care to the sports teams at each institution notified the study coordinator when an ACL injury occurred. The study coordinator then contacted the potential participant, described the study, evaluated eligibility criteria, and invited the eligible athlete to participate.

Subjects were eligible for the study if they were injured during participation in an above-mentioned sport at the participating schools, the injury was produced by a noncontact mechanism (defined as an injury that did not involve direct impact to the knee), and they had not previously suffered an ACL injury (on either side). At the time of enrollment of an injured subject, control subjects of same age and sex were randomly selected from the injured subject's teammates and were invited to take part in the study. This approach ensured that the injured athletes and controls would have similar exposure to the sport activity associated with the injury. As for injured subjects, those with prior ACL injury were not eligible to be selected as controls. The goal was to enroll 3 control subjects for each injured subject; however, the statistical analysis did not require that all injured athletes have an equal number of controls, so fewer controls were used if 3 were not available or willing to participate.

After injury but before undergoing ACL reconstruction, the injured subjects and matched controls visited our laboratory for the purpose of undergoing measurement of potential risk factors. This study focused on variables that could be measured with field-based techniques and thus had the potential to be used to screen large numbers of subjects, rather than those that needed to be obtained from radiographs or magnetic resonance imaging. Five categories of risk factors were characterized: demographic characteristics, joint laxity (knee, ankle, and generalized), lower extremity alignment, strength (trunk, hip, knee, and ankle), and personality characteristics (evaluated with the Temperament and Character Inventory).[12] The methods used to obtain these measurements are summarized in the Appendix (available online). The same investigator interviewed all study participants and documented 16 demographic characteristics: family history of ACL injury, presence of chronic disease (75% of injured participants reported suffering from chronic asthma), race, weight, height, body mass index (BMI), hours spent participating in sport per week, number of years participating in sport, use of braces, use of medication, limb dominance, prior leg surgery, and prior injury to the lower extremity (knee, hip/thigh, lower leg, or ankle/foot). Eleven lower extremity alignment measurements were made by the same examiner on all participants, and a description of how these measurements were made and their reliability have been published[26] (see the Appendix): passive and active genu recurvatum, hamstring extensibility, standing quadriceps angle in the coronal plane, navicular drop, tibiofemoral angle in the coronal plane, pelvic angle, tibial torsion, hip anteversion, and length of the tibia and femur. Knee, ankle, and generalized joint laxity were characterized by 5 measurements, and these were made by the same individual on all participants. The KT-1000 arthrometer was used to measure the anterior-posterior load-displacement (anterior-posterior laxity and the anterior and posterior stiffness) response of the knee; clinical examination with the talar tilt test was used to evaluate ankle laxity; and the Beighton test was used to evaluate generalized joint laxity.[3] Details on how knee, ankle, and trunk strength measurements were made and their reliability are provided in the Appendix. Knee muscle strength (flexion and extension evaluated at 15° and 30° of flexion) and ankle muscle strength (flexors and extensors) were measured with the Biodex System II. Isometric trunk strength (flexion and extension) was measured with the Cybex System II. These methods have been described, and specific details are provided in the online Appendix.[16] The methods used to measure isometric hip strength (flexion, extension, abduction, adduction, internal and external rotation) were those developed by Tourville et al.34 The same investigator measured strength for all subjects, and the peak torque developed during the test was used as the outcome. Personality characteristics were evaluated with the Temperament and Character Inventory,[12] which was completed by the study participants. These data were used to determine the participants' temperament (classified in 4 dimensions: Novelty Seeking, Harm Avoidance, Reward Dependence, and Persistence) and character (classified in 3 dimensions: Self-directedness, Cooperativeness, and Self-transcendence).

**Statistical Analysis**

Prior work has found that an athlete's sex, sport, and level of play have independent effects on the risk of suffering ACL injury.[8] Control subjects were therefore selected from among each case's teammates to control for age, sex, sport, and level of play, as well as extrinsic conditions, such as the playing surface, environmental factors, and time at risk in the statistical analysis. The strength variables were analyzed as peak torque (N·m), peak torque normalized to body weight (N·m/kg), and peak torque adjusted for body weight as a covariate in the regression equation. Results for all 3 analyses were similar, but it is difficult to assess the association between strength and ACL injury risk through the normalized variables because of a strong relationship between body weight and risk of ACL injury. The normalized results are therefore not presented. All analyses were performed separately for males and females because the univariate analyses (see the Appendix for details) demonstrate that the risk factors for noncontact ACL injury differ between the sexes.

Data from injured subjects and matched controls from the same athletic team were analyzed with multivariate conditional logistic regression to examine the effects of combinations of variables on the risk of suffering noncontact ACL injury and to construct statistical risk models. Because of the large number of potential risk factors measured in the study, multivariate analyses were conducted in 2 steps. First, models were fitted to each of 4 categories of risk factors (joint laxity, lower extremity alignment, strength, and personality characteristics) through both forward and backward stepwise variable selection procedures to identify sets of predictors that had significant ($P < .05$) independent associations with injury risk. For the fifth category, demographic characteristics, only a forward stepwise procedure was used because most of the variables are dichotomous and the maximum likelihood procedure for fitting the regression models did not converge when all variables were simultaneously included in the analysis. For all other categories of variables, the forward and backward stepwise procedures yielded the same risk models. However, it is possible for important predictors to be excluded from a model because of their associations with ≥1 variables in the model at an intermediary step in the selection process. To verify that this did not occur, all omitted variables were individually added to the final model, but none had significant independent associations with injury risk.

The independent risk factors identified from the multivariate analyses of each category of variables were then analyzed together to obtain the final risk models. To avoid overfitting the data and improve the generality robustness of the results, only variables with a significance level of $P < .02$ were retained in the final risk models. All analyses were conducted separately for males and females. Again, both forward and backward variable selection procedures were used, which produced the same results.

For most variables, only a few subjects had missing data. This represents a concern for multivariate analysis, as data must be available for all variables in the model, leading to the exclusion of larger numbers of subjects and raising concern about potential selection bias. To evaluate the effect of excluding subjects with missing data, the risk models derived for subjects with nonmissing data were fitted to the data from all subjects, using multiple imputation of missing data. In this approach, the fully conditional specification method was used to obtain regression estimates for each missing value based on the observed values of nonmissing variables and a random component reflecting the uncertainty in the estimate. Ten data sets with different imputed values were generated, and each was analyzed with conditional logistic regression to fit the risk models obtained when complete data were used. The estimated regression coefficients obtained from each of the 10 data sets were then combined with the inference methods for multiple imputation described by Little and Rubin to obtain the final regression model.[21] In addition to reducing bias, this method has the advantage of maximizing power by utilizing all available data while taking into account the uncertainty inherent in the imputed values.

In addition, univariate conditional logistic regression was conducted to allow us to compare the findings from our study to prior reports in the literature, as most of what has been reported has focused on one or a small selection of potential risk factors. These data are presented in the Appendix.

## RESULTS

A total of 130 ACL-injured athletes meeting the study entry criteria were identified, and 109 (78.4%) were recruited into the study. Injured subjects who were not enrolled included those for whom no controls could be recruited (8 subjects), those who were not interested in the study because they believed it was of no value to them (7 subjects) or did not respond to invitations to participate (1 subject), and those who were unable to travel to our research center for the purpose of data collection before undergoing surgery (5 subjects). Thirty-two injured athletes had 1 control recruited into the study; 38 had 2 controls; 37 had 3 controls; and 2 athletes had 4 controls—for a total of 227 controls. The characteristics of the study participants and the conditions associated with the injury are summarized in Table 1. The 109 injured subjects ranged from 14 to 23 years of age, with a majority of the participants (75%) between the ages of 15 and 20 years. Seventy (64.2%) injured subjects were female; 65% were in high school; and 75% were participating in soccer, basketball, or lacrosse at the time of injury. A majority of the injuries occurred in season (70%) during a game (76%), and the injuries were equally distributed between home and away venues. The injuries occurred while participating in a sport on natural turf (47%), artificial turf (26%), or a wood court inside (23%) (Table 1).

For the male athletes, 2 of the 16 demographic variables were found to have significant multivariate associations with ACL injury risk: having a parent who suffered an ACL injury and having a chronic disease were jointly associated with increased ACL injury risk (Table 2). After adjustment for the combined effects of these 2 risk factors, none of the other demographic variables were significantly related to ACL injury risk. Of the 5 joint laxity variables, 3 had significant multivariate associations with ACL injury risk in the males: increases in anterior-posterior knee laxity, posterior knee stiffness, and Beighton score were jointly predictive of increased risk of injury (Table 2). Of the 11 measurements of lower extremity alignment, the combination of decreased standing quadriceps angle and increased navicular drop were associated with increased risk of suffering an ACL injury (Table 2). After adjustment for hip adduction strength, which had a significant inverse relationship with risk of injury, no other strength variables were associated with the risk of suffering ACL injury in males (Table 2). Multivariate analysis of the personality characteristics found no significant associations with risk of injury for male athletes. For most categories of variables, the odds ratios and significance levels obtained when the risk models were fitted to data from all male subjects, based on multiple imputation of missing values, were very similar to those based on subjects with complete data (Table 2). For the demographic risk factors, however, the odds ratio associated with having a chronic disease was somewhat reduced when all cases were included.

TABLE 1
Descriptive Information on ACL-Injured Subjects and the Conditions Under Which the Trauma Occurred[a]

| Variable | n (%) |
|---|---|
| Sex | |
| Male | 39 (35.8) |
| Female | 70 (64.2) |
| Age group, y | |
| 14 | 10 (9.2) |
| 15-16 | 32 (29.4) |
| 17-18 | 35 (32.1) |
| 19-20 | 15 (13.8) |
| 21-23 | 17 (15.6) |
| Sport associated with injury | |
| Soccer | 39 (35.8) |
| Basketball | 25 (22.9) |
| Lacrosse | 18 (16.5) |
| Field hockey | 5 (4.6) |
| Football | 7 (6.4) |
| Rugby | 7 (6.4) |
| Volleyball | 2 (1.8) |
| Baseball/softball | 1 (0.9) |
| Track and field | 2 (1.8) |
| Wrestling | 1 (0.9) |
| Frisbee | 2 (1.8) |
| Level of play at time of injury | |
| High school | 71 (65.1) |
| College | 38 (34.9) |
| Surface at the time of injury | |
| Artificial turf | 28 (25.7) |
| Inside court | 25 (22.9) |
| Natural turf | 51 (46.8) |
| Other | 5 (4.6) |
| Activity when injury occurred | |
| Game | 83 (76.1) |
| Practice | 26 (23.9) |
| Season when injury occurred | |
| In season | 76 (69.7) |
| Preseason | 23 (21.1) |
| Postseason | 10 (9.2) |
| Location at the time of injury | |
| Away | 47 (43.1) |
| Home | 62 (56.9) |

[a]Data are presented for the anterior cruciate ligament (ACL)–injured subjects. The data for the control subjects are the same, as they were matched with the ACL-injured subjects according to sex, the team on which they played (sport), and level of play.

TABLE 2
Analysis of Data Obtained From the Male Study Athletes[a]

| Variable | Nonmissing Data Only OR (95% CI) | Nonmissing Data Only *P* | Multiple Imputation of Missing Data OR (95% CI) | Multiple Imputation of Missing Data *P* |
|---|---|---|---|---|
| Demographic characteristics (n = 37) | | | | |
| Parent with ACL injury | 7.97 (1.71-37.2) | .008 | 7.50 (1.57-35.92) | .012 |
| Chronic disease | 8.46 (1.85-38.6) | .006 | 6.44 (1.59-26.07) | .009 |
| Joint laxity (n = 38) | | | | |
| Anterior-posterior knee displacement, mm | 1.31 (1.03-1.68) | .031 | 1.33 (1.04-1.70) | .025 |
| Beighton score | 1.34 (1.06-1.70) | .025 | 1.33 (1.06-1.68) | .016 |
| Posterior stiffness of the knee, N/mm | 1.18 (1.02-1.37) | .013 | 1.18 (1.02-1.37) | .025 |
| Lower extremity alignment (n = 38) | | | | |
| Navicular drop, mm | 1.19 (1.06-1.34) | .003 | 1.20 (1.07-1.35) | .003 |
| Standing quadriceps angle, deg | 0.81 (0.70-0.93) | .004 | 0.80 (0.69-0.93) | .002 |
| Strength (n = 34) | | | | |
| Hip adduction (10 N·m) | 0.79 (0.67-0.93) | .006 | 0.80 (0.69-0.93) | .004 |

[a]Presented is the multivariate analysis of each category of variables: Data are presented for analysis of all nonmissing data and multiple imputation of missing data. Odds ratios (ORs) are presented for changes in the following risk factors: demographic characteristics (having a parent with an anterior cruciate ligament [ACL] injury, presence of a chronic disease), joint laxity (for a unit change of the risk factors), lower extremity alignment (for a unit change of the risk factors), and strength (for a 10-N·m change in hip adduction strength).

In multivariate analysis of the demographic data from the female athletes, increased BMI, having a parent who had suffered an ACL injury, and, in contrast to the males, not having a chronic disease were associated with increased risk of suffering a first-time noncontact ACL injury (Table 3). As was the case for the males, increased anterior-posterior knee laxity was related to increased risk of injury, but after adjustment for the effect of this variable, none of the other laxity variables were significantly associated with ACL injury risk in females (Table 3). Among the measures of lower extremity alignment, increased navicular drop and increased passive genu recurvatum had significant multivariate associations with ACL injury risk in female athletes (Table 3). Multivariate analysis of strength measurements from the female athletes found that increased hip and trunk flexion strength and decreased hip adduction strength were jointly associated with increased risk of ACL injury (Table 3). When the risk models were fitted with multiple imputation of missing data, having a chronic disease was no longer significantly associated with a decreased risk of ACL injury (Table 3). The odds ratios for the strength measurements were also attenuated when the model was fit with multiple imputation of missing data. Multiple imputation was not required for the lower extremity alignment variables, because no subjects had missing data. It could not be used for the personality characteristic data, because subjects had data for either all variables or none, in which case there were no data on which to base the imputation.

TABLE 3
Analysis of Data Obtained From the Female Study Athletes[a]

| Variable | Nonmissing Data Only | | Multiple Imputation of Missing Data | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| Demographic characteristics (n = 66) | | | | |
| Parent with ACL injury | 4.69 (1.78-12.34) | .002 | 4.11 (1.57-10.74) | .004 |
| Body mass index | 1.20 (1.04-1.38) | .013 | 1.20 (1.04-1.37) | .011 |
| Chronic disease | 0.38 (0.15-0.97) | .044 | 0.52 (0.23-1.22) | .135 |
| Joint laxity (n = 66) | | | | |
| Anterior-posterior knee displacement, mm | 1.27 (1.12-1.45) | <.001 | 1.25 (1.10-1.43) | <.001 |
| Lower extremity alignment (n = 70) | | | | |
| Navicular drop, mm | 1.09 (1.01-1.18) | .038 | | |
| Passive genu recurvatum, deg | 0.90 (0.83-0.97) | .004 | | |
| Strength (n = 58) | | | | |
| Hip adduction (10 N·m) | 0.67 (0.51-0.88) | .003 | 0.75 (0.58-0.98) | .038 |
| Hip flexion (10 N·m) | 1.38 (1.12-1.70) | .003 | 1.21 (1.00-1.48) | .054 |
| Trunk flexion (10 N·m) | 1.28 (1.08-1.51) | .004 | 1.19 (1.03-1.38) | .021 |
| Personality characteristics (n = 65) | | | | |
| Reward dependence (5 units) | 0.83 (0.71-0.96) | .013 | | |

[a]Presented is the multivariate analysis of each category of variables. Data are presented for analysis of all nonmissing data and multiple imputation of missing data. Note that multiple imputation of missing data were not conduced to the lower extremity alignment data because a complete data set was acquired on all study participants. Odds ratios (ORs) are presented for changes in the following risk factors: demographic characteristics (having a parent with an anterior cruciate ligament [ACL] injury, presence of chronic disease, and a 1-unit change in body mass index), joint laxity (a 1-mm change in anterior-posterior displacement), lower extremity alignment (a unit change in navicular drop and passive genu recurvatum), strength (a 10-N·m change in hip adduction, hip flexion, and trunk flexion), and personality characteristics (a 5-unit change in reward dependence).

## Final Risk Model for Male Athletes

For males, multivariate analysis of the significant variables presented in Table 2 yielded an overall model for ACL injury risk that included 2 measures of knee biomechanics (anterior-posterior knee laxity and posterior stiffness of the knee) and 2 measures of lower extremity alignment (standing quadriceps angle and navicular drop) (Table 4). All 4 variables had highly significant independent associations with injury risk, and their odds ratios indicated that male athletes with decreased standing quadriceps angle and increased navicular drop, anterior-posterior knee laxity, and posterior stiffness of the knee were at highest risk for ACL injury (Table 4). The same model was obtained regardless of whether a forward or backward stepwise procedure was used for variable selection and whether or not the strength variable (hip adduction strength) was included. When the model was fitted with multiple imputation of missing values, the odds ratios and significance levels were very similar to those based on subjects with complete data (Table 4).

TABLE 4
Male Multivariate Model for Risk of Noncontact Anterior Cruciate Ligament Injury[a]

| Variable | Nonmissing Data Only | | | | Multiple Imputation of Missing Data | | | |
|---|---|---|---|---|---|---|---|---|
| | Beta | SE | OR (95% CI) | *P* | Beta | SE | OR (95% CI) | *P* |
| Anterior-posterior displacement of the knee, mm | 0.436 | 0.165 | 1.55 (1.19-2.14) | .008 | 0.447 | 0.165 | 1.56 (1.13-2.16) | .007 |
| Posterior stiffness of the knee, N/mm | 0.285 | 0.101 | 1.33 (1.09-1.62) | .005 | 0.295 | 0.102 | 1.34 (1.10-1.64) | .004 |
| Navicular drop, mm | 0.226 | 0.079 | 1.25 (1.07-1.46) | .004 | 0.234 | 0.079 | 1.26 (1.08-1.48) | .003 |
| Standing quadriceps angle, deg | −0.270 | 0.094 | 0.76 (0.64-0.92) | .004 | −0.275 | 0.095 | 0.76 (0.63-0.91) | .004 |

[a]Data are presented for full analysis of all nonmissing data and multiple imputation of missing data. Odds ratios (ORs) are presented for a unit change in the risk factor.

**Final Risk Model for Female Athletes**

For females, when all significant risk factors presented in Table 3 were included in a multivariate analysis, the resulting risk model indicated that having a parent who had suffered an ACL injury, increased anterior-posterior knee laxity, and increased trunk flexion strength were jointly associated with increased risk of suffering an ACL injury (Table 5, statistical model 1). A similar model was obtained when the strength variable was excluded from the analysis, except that BMI entered the model instead of trunk flexion strength (Table 5, statistical model 2). Increased BMI, with increased anterior-posterior knee laxity and having a parent who had suffered an ACL injury, was associated with increased ACL injury risk. Forward and backward stepwise variable selection procedures yielded the same 2 models, and when the analyses were based on multiple imputation of missing data, the odds ratios and significance levels were very similar to those based on subjects with complete data, except for having a parent with an ACL injury. In particular, the odds ratio associated with having a parent with an ACL injury fell from 4.99 to 3.84 in model 1 and from 4.59 to 3.80 in model 2 when the analysis included all subjects and values were imputed for missing data.

TABLE 5
Female Multivariate Model for Risk of Noncontact ACL Injury[a]

| Variable | Nonmissing Data Only | | | | Multiple Imputation of Missing Data | | | |
|---|---|---|---|---|---|---|---|---|
| | Beta | SE | OR (95% CI) | *P* | Beta | SE | OR (95% CI) | *P* |
| Model 1 | | | | | | | | |
| Parent with ACL injury | 1.608 | 0.540 | 4.99 (1.73-14.37) | .003 | 1.346 | 0.498 | 3.84 (1.45-10.20) | .007 |
| AP knee displacement, mm | 0.226 | 0.072 | 1.25 (1.09-1.44) | .002 | 0.208 | 0.07 | 1.23 (1.07-1.41) | .003 |
| Trunk flexion strength (10 N·m) | 0.229 | 0.082 | 1.26 (1.07-1.48) | .005 | 0.174 | 0.073 | 1.19 (1.03-1.37) | .018 |
| Model 2 | | | | | | | | |
| Parent with ACL injury | 1.525 | 0.529 | 4.59 (1.63-12.95) | .004 | 1.334 | 0.507 | 3.80 (1.40-10.27) | .009 |
| Body mass index | 0.182 | 0.076 | 1.20 (1.03-1.39) | .017 | 0.199 | 0.073 | 1.22 (1.06-1.41) | .007 |
| AP knee displacement, mm | 0.232 | 0.071 | 1.26 (1.10-1.45) | .001 | 0.218 | 0.069 | 1.24 (1.09-1.43) | .002 |

[a]Data are presented for full analysis of all nonmissing data and multiple imputation of missing data. Odds ratios (ORs) are presented as follows: for model 1 (having a parent with prior anterior cruciate ligament [ACL] injury, a 1-mm change in anterior-posterior [AP] knee displacement, and a 10-N·m change in trunk flexion strength), and for model 2 (having a parent with prior ACL injury, a 1-unit change in body mass index, and a 1-mm change in AP knee displacement).

## DISCUSSION

The findings from this investigation support the hypothesis that a diverse combination of risk factors predispose athletes to ACL injury and that separate risk models are needed to assess the risk of first-time ACL injury risk in males and females. When male athletes as a group were considered, the multivariate risk model included the combination of increased anterior-posterior knee laxity, posterior knee stiffness, and navicular drop and decreased standing quadriceps angle as predictive of suffering a first-time noncontact ACL injury. For females, the combined effects of increased anterior-posterior knee laxity, increased BMI, and having a parent who had suffered an ACL injury were predictive of ACL injury. A similar model that included trunk flexion strength instead of BMI was equally predictive of ACL injury in females, with increased trunk flexion being associated with a higher risk of injury. This model may be less useful because trunk flexion is more difficult to measure than BMI. The results obtained when data from all subjects were used and missing values imputed were similar to the results based only on subjects with no missing data. However, we recommend using the estimates based on multiple imputation of missing data because they are less subject to bias. Although both male and female risk models include anterior-posterior knee laxity as a predictor of ACL injury, they are otherwise dissimilar. We applied the risk model derived for males to the data obtained from the females and found that none of the multivariate associations with risk were statistically significant. Similarly, when the female risk model was applied to the data obtained from the males, only parental history of ACL injury was statistically significant. This supports our hypothesis that separate models are needed to assess the risk of first-time ACL injury in males and females.

This prognostic investigation provides evidence that different sets of characteristics place males and females at increased risk of suffering ACL injury, and this supports the hypothesis that the intrinsic mechanism(s) responsible for producing ACL injuries differs between the sexes. If this hypothesis is true, it would suggest that different approaches may be needed to identify males and females at increased risk for suffering ACL injury and that different intervention programs may be required for each sex to reduce the likelihood of suffering this debilitating injury. It is also important to point out that this investigation established one risk factor that was similar between the sexes: increased anterior-posterior knee laxity was associated with increased risk of injury. Since increased anterior-posterior knee laxity is associated with increased peak ACL strain values produced during landing from a jump—a direct measure of ACL biomechanics during an activity that has been shown to be associated with increased risk of ACL trauma[19]—this provides evidence in support of an alternative hypothesis that the intrinsic mechanism(s) responsible for producing ACL injuries has at least one similarity between the sexes: increased anterior-posterior joint laxity and the peak ACL strain values developed during activities that challenge the knee and ACL, such as landing from a jump. When the before-mentioned hypotheses are evaluated, the finding that males and females have only some ACL injury risk factors in common raises concerns about data analyses based on combined data from males and females. This approach may obscure the effects of some risk factors or find apparent associations with injury for other variables simply because they differ between the sexes.

Within each category of potential risk factors (demographic characteristics, joint laxity, lower extremity alignment, strength, and personality characteristics), most variables that had significant univariate associations with risk of suffering a first-time noncontact ACL injury were found to have independent effects when analyzed in combination (see the Appendix for the univariate data). There were, however, a few exceptions. Among males, weight was not significantly associated with risk of injury after adjustment for chronic disease and parental history of ACL injury. Likewise, for males, passive genu recurvatum was not significantly associated with risk of injury after adjustment for navicular drop and standing quadriceps angle. When female athletes as a group were considered, neither the Beighton assessment of generalized joint laxity nor posterior knee stiffness was significantly related to risk after adjustment for the effect of anterior-posterior knee laxity. Similarly, for the females, active genu recurvatum was not significant after adjustment for passive genu recurvatum, with which it was highly associated.

In contrast, several variables did not have significant univariate associations with ACL injury risk but were significant when considered in combination with other variables (see the Appendix for the univariate data). In males, increased posterior knee stiffness was significantly associated with injury risk after adjustment for anterior-posterior laxity of the knee. Although this may seem counterintuitive, posterior stiffness and anterior-posterior laxity are negatively correlated, and each of their associations with risk was increased after adjustment for the other variable.

This indicates that the variability of case-control differences in anterior-posterior laxity was reduced by controlling for posterior knee stiffness and vice versa, providing better risk prediction than what would be obtained based on their individual effects. In females, both hip adduction and hip flexion strength were associated with injury risk when adjusted for each other and trunk flexion strength but not in univariate analyses.

Despite its strong univariate association with ACL injury risk (see the Appendix for details), having a parent who had suffered an ACL injury was not predictive of injury in males after anterior-posterior knee laxity and lower limb alignment were taken into account. This finding suggests that there may be a prominent genetic influence on knee laxity and limb alignment in males and that these characteristics mediate the effect of having a parent who had suffered an ACL injury. In contrast, among females, a parental history of ACL remained a strong predictor of risk after adjustment for the anterior-posterior knee laxity and lower extremity alignment variables. This finding introduces the hypothesis that the genetic determinants of these characteristics differ in males and females. Alternatively, the effects of the knee laxity and alignment variables may differ in men and women because of their different anatomic characteristics and/or different injury mechanisms. In either case, none of the variables measured in our study appears to explain the increased risk of ACL injury in females who have a parent who suffered the same injury.

Prior research has found menstrual cycle phase at the time of ACL injury (used as an indirect indicator of acute sex hormone concentrations) to be associated with risk of suffering this trauma,[6] and consequently, when designing our study, we planned to determine the phase of the menstrual cycle at the time of ACL injury and include it as a potential risk factor for injury. An approach to characterize menstrual cycle phase with the use of salivary progesterone from a sample obtained after injury was developed; however, we found that it was not accurate.[33] Therefore, we did not attempt to measure cycle phase at the time of injury and use it as a potential ACL injury risk factor. At the current time, the analysis of serum obtained immediately after ACL trauma is the only approach that has been shown to be effective at documenting acute sex hormone concentrations at the time of injury.[6] This was not possible in the current study, as we recruited subjects from a large region and did not have access to them immediately after injury for the purpose of enrolling them (and their matched controls) in the study and obtaining a serum sample.

Uhorchak et al[35] conducted a study that derived multivariate risk models for noncontact ACL injury, and, unlike us, they obtained similar models for male and female cadets at the US Military Academy. Their model for females also included increased anterior-posterior knee laxity and increased BMI and was much more predictive of risk than their model for males. Both their male and female models included increased generalized joint laxity (also evaluated with the Beighton test) and decreased femoral notch width (measured from plain film radiographs) associated with increased risk of suffering ACL injury. Our results are not directly comparable with those of Uhorchak et al because of differences in the risk factors considered for the multivariate analyses, most notably their inclusion of radiographic measurements of femoral notch geometry. In addition, our study included both high school and college athletes, and in our study design we adjusted for this, the athlete's sex, and the type of sport, as they have independent effects on the risk of suffering ACL injury.[8] Our study also had >4 times as many injured subjects. Nevertheless, it is noteworthy that, unlike Uhorchak et al, we found different risk models for males and females. Simon et al[27] and Sturnick et al[31] evaluated the combined effects of multiple measures of knee geometry on the risk of suffering ACL injury. Simon et al reported that subjects who suffered an ACL injury had a lateral tibial plateau with a significantly greater posterior-inferior directed slope and a smaller femoral notch as compared with those who did not suffer injury. Sturnick et al also found that combinations of knee joint geometry measurements provided more information about the risk of noncontact ACL injury than individual measures and that the aspects of geometry that best explained the relationship between knee geometry and the risk of injury in males (decreased ACL volume and a decrease in the lateral compartment posterior meniscus to subchondral bone wedge angle) differed from those that were predictive of injury in females (decreased width of the femoral notch at its anterior outlet and increased posterior-inferior slope of the lateral compartment articular surface).

This was a prospective cohort study with a nested case-control sampling and statistical analysis. An important strength of this approach is that the case-control sampling was nested within a prospective study that controlled for exposure to the at-risk activities associated with injury. As a consequence, the odds ratios obtained from the conditional logistic regressions are mathematically comparable with the estimates of relative risk that would be obtained from a prospective study design in which all in a cohort are followed over time and the data are used in a Cox regression analysis to model time to injury for all athletes, with risk-set stratification based on the participating teams.[10] Another important strength of the nested case-control study design is that cases and controls were selected from the same athletic team because our goal was to obtain models that would predict which individual on a team is at increased risk of suffering an ACL injury when compared with his or her teammates. We believe that this is more meaningful for athletes, coaches, and licensed athletic trainers because preventive interventions are most likely to be implemented at the team level. An athlete's relative risk of sustaining a first-time noncontact ACL injury can be computed by subtracting the team average for each continuous variable in the risk model from his or her measurement, multiplying the result by the beta coefficients shown in Tables 4 and 5, and summing across all variables. (In the model for females, the beta coefficient for the parental history of ACL injury would be added to the sum if the risk factor was present.) The antilog of this sum ($e^x$) will be the athlete's risk of injury relative to a teammate with the average values of the risk factors and, for females, no parental history of ACL injury. The models can also be used to compute an athlete's absolute risk of a first-time noncontact ACL injury while participating in his or her sport by multiplying his or her relative risk by the injury rate among athletes of the same sex, playing the same sport at the same level of competition.[13,20] Estimates of these injury rates have been published.[8] For this calculation, the average values of the risk factors in the athletes on whom the injury rates were based should be used to compute relative risk. Although these normative values are unknown at present, the mean values for the controls in our study likely provide a reasonable estimate. A potential weakness of our approach is that the risk factors were measured after injury and some (eg, measurements of joint laxity, the strength of the extensors and flexors of the knee, and genu recurvatum) may have been altered by the trauma that tore the ligament. Consequently, we measured the uninjured, normal knee of subjects who suffered an ACL injury and considered it representative of the injured limb before injury. In prior research of subjects with normal knees that had not suffered a prior injury, researchers found that the variability in joint laxity, strength, and genu recurvatum between legs is small, indicating that the measurements made on the uninjured limb are valid proxy measures for the injured limb before the trauma.4 We considered a prospective approach that measured potential risk factors before injury and thus did not require this assumption, but we determined that it was not feasible, because it would have required preparticipation/preinjury measurements of all variables to be made on >8000 athletes from all teams across all participating institutions to produce the same number of noncontact injuries that were generated in the current study. In addition, a prospective approach assumes that no changes in the potential risk factors occur between the time they are measured (typically done in the preseason before exposure to organized sport) and the time of injury, which may not be a valid assumption for some measurements. This is of concern for the potential risk factors that are known to change during and between sports seasons, such as strength. Another potential weakness associated with the study was the unbalanced sample size. Throughout the study, we made every effort to recruit and retain an equal number of males and females; nonetheless, we enrolled almost twice as many injured females (70) as males (39). This was attributed to the incidence rate of injury being greater in females than males for the sports that were studied[8] and to a substantially larger proportion of the male participants and their potential controls who were unwilling to participate because they believed that the study would be of no value to them. At a significance level of 0.05, the sample sizes in the study provided 80% power to detect odds ratios of 3.0 and 2.2 in males and females, respectively, for dichotomous variables with moderate (30%) prevalence. For variables with lower (10%) prevalence, the detectable odds ratios are 4.0 and 2.8 in males and females, respectively. The study also had 80% power to detect odds ratios of 1.6 and 1.4 per each standard deviation of increase in continuous variables for males and females, respectively. Some variables examined in the study may have weaker associations with ACL injury risk that were not detected. However, they would have less prognostic value, and the primary aim of our study was to identify factors that are potentially useful for risk assessment.

For the models to be useful as screening tools for large numbers of high school and college athletes, it must be feasible to quickly and accurately measure their risks factors. The models for both males and females included KT-1000 arthrometer measurement of anterior-posterior knee laxity, and while the use of the KT-1000 as a prognostic tool is certainly feasible, it requires someone who is trained in its application. For females, substituting generalized joint laxity as measured by the Beighton score (a measurement that is easier and faster to make) for anterior-posterior knee laxity yielded a similar risk model, although the fit to the data was not as good and, hence, the risk estimates based on the model are likely to be less accurate. The other 2 risk factors in model 2 for females (having a parent who suffered an ACL injury and BMI) can be measured with less difficulty. In addition to anterior-posterior knee laxity, the risk model for males includes posterior stiffness (which is also measured with the KT-1000), navicular drop, and standing quadriceps angle. As highlighted above for application of the KT-1000, measurement of navicular drop and standing quadriceps angle requires a person who has undergone a certain amount of training to make these measurements. If both anterior-posterior knee laxity and posterior stiffness are replaced with the Beighton score for the male data, the resulting model has a much poorer fit to the data. A simpler method for acquiring measurements comparable with those obtained with the KT-1000 arthrometer would therefore enhance the usefulness of the risk models.

The validity of the relative and absolute risk estimates based on our injury risk models is, of course, dependent on the validity of the models themselves; therefore, a prospective application of the models to teams of athletes is needed to assess how well they predict ACL injury. Once their validity as screening tools has been established, the risk models developed in this investigation can be used in the field to identify those at increased risk for injury, so intensive preventive programs can be targeted at them. This approach will allow valuable resources to be targeted at those who are at greatest risk of injury, rather than targeting the overall population at risk with the hope of helping the minority that are most likely to suffer ACL injury. In addition, the risk models could facilitate clinical studies of new interventions and prevention strategies by focusing on high-risk individuals, rather than all participants in sports that are known to be associated with ACL injury. Since noncontact ACL injury is a relatively rare event in comparison with other ligament injuries, such as lateral ankle ligament sprains,[7] this approach would allow prevention studies to assess an intervention's effectiveness in reducing noncontact ACL injury rates by recruiting and following a smaller number of athletes over shorter intervals.

In summary, this study demonstrated that combinations of factors provide more information about an athlete's risk of suffering an ACL injury than individual risk factors and that separate models are needed for assessing risk of injury in males and females. The models derived as part of the study provide potentially useful screening tools for identifying athletes at increase risk of injury.

## FOOTNOTES

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