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# Effect of Age at Menarche on Anterior Cruciate Ligament Injury Incidence and Anterior Knee Laxity in Collegiate Athletes

## Cover Page Footnote

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# *Effect of Age at Menarche on Anterior Cruciate Ligament Injury Incidence and Anterior Knee Laxity in Collegiate Athletes*

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**Background:** Female athletes suffer painful, costly, and career-limiting non-contact anterior cruciate ligament (ACL) injuries more often than males. Previous research suggests that pubertal neuromusculoskeletal development contributes to this sex-bias, but the manner in which variation in pubertal development affects injury risk within females is poorly understood. Age at menarche is a variable, significant pubertal developmental event, signaling the onset of estrogen cycling and affecting musculoskeletal development. Earlier menarche may increase injury risk, possibly by increasing anterior knee laxity through prolonged estrogen exposure. **Purpose:** The purpose of this case-control study was to test the primary hypothesis that collegiate athletes with previous ACL injuries have earlier age at menarche than their uninjured peers, and to test the secondary hypothesis that earlier menarche is related to greater anterior knee laxity in injured and uninjured athletes. **Methods:** The study sample consisted of female NCAA Division-I varsity athletes (N=14 injured, N=120 uninjured). Outcome measures included: menstrual history and ACL injury details (injury age, activity at time of injury, contact vs. non-contact), assessed by questionnaire; and anterior knee laxity assessed by KT-1000 arthrometer. Correlation, t-tests, and regression analysis were used to test for associations between age at menarche, injury incidence, and knee laxity. **Results:** Fourteen athletes reported ≥1 non-contact ACL injury, and had significantly earlier menarche than uninjured athletes (12.6±1.3 y vs. 13.4±1.4 y; P=0.05). Earlier menarche also significantly predicted injury status (Wald $\chi^2$=7.43; P<0.01; b=-1.02±0.37; OR=0.36; 95% CI: 0.17-0.75) but was not correlated with anterior knee laxity. Within injured athletes, however, laxity in the unaffected knee was significantly related to time since menarche ($r^2$=0.79; P<0.01) and estimated number of cycles ($r^2$=0.72; P<0.01). Conclusions: These results suggest that earlier menarche is a moderate risk factor for non-contact ACL injury in female collegiate athletes, potentially through effects on ligament laxity. Age at menarche may be an important variable to include as part of the injury risk screening process. ***Keywords:*** *Anterior Cruciate Ligament, Age at Menarche, Injury Risk, Puberty, Arthrometry*

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## *INTRODUCTION*

Non-contact anterior cruciate ligament (ACL) injuries are painful, costly to repair and rehabilitate, and lead to loss of playing time, reduced physical activity, and increased knee osteoarthritis risk.[1] There is considerable public health interest in prevention of ACL injuries through neuromuscular retraining interventions.[2,3] Such interventions, however, are also associated with costs in terms of time, money, and effort on the part of athletes and clinicians.[4] Intervention efficacy can be maximized by targeting high-risk individuals and focusing on primary injury mechanisms.[4] Still, efforts to identify individuals at elevated risk are complicated by the multifactorial nature of non-contact ACL injury etiology and inter-individual variation in risk factors, even within known high-risk cohorts.[5]

Some of the inter-individual variation in risk may be driven by differences in the process of pubertal development. Several ACL injury risk factors emerge or are exacerbated during puberty, with injury rates in both sexes increasing around puberty and remaining high well into young adulthood.[6-8] Females, however, sustain ACL injuries more frequently than males playing the same sports, and this sex-based disparity in injury rates also emerges during puberty.[7,9,10] Divergent pubertal developmental trajectories in males and females likely underlie a suite of high-risk traits that appear widely in post-pubertal females, but less commonly in males.[11-20]

Despite these broad sex-based distinctions, the process of puberty in terms of rates and timing of growth events is highly variable within each sex. Variation in pubertal development may therefore have effects on variability in ACL injury risk factors within females. Our previous work[21] showed that individual-level variation in pubertal timing, specifically earlier age at menarche, was related to biomechanical profiles consistent with higher female ACL injury risk. Menarche is the onset of menses, marking the end of the pubertal growth spurt and initiating the cessation of long bone linear growth.[22,23] Earlier menarche curtails musculoskeletal development at younger ages, and may therefore have important effects on skeletal alignment, neuromuscular control, and biomechanical phenotypes associated with non-contact ACL injuries.

In addition to apparent effects on neuromusculoskeletal development, earlier menarche may also increase injury risk by impacting ligament laxity. The onset of estrogen cycling with menses can weaken ligament structure by affecting collagen metabolism, thereby increasing laxity and injury risk.[24-28] Consistent with estrogen's effects on ligament structure, post-pubertal females tend to have greater joint laxity than males, and female non-contact ACL injuries are more common during the higher-estrogen, peri-ovulatory and mid-luteal phases of the menstrual cycle.[17,29-34] From a biomechanical perspective, cyclical increases in laxity are associated with a shift to higher-risk knee kinematics during jump landing tests.[35] Thus, by potentially extending the period of exposure to higher estrogen levels, earlier menarche may increase injury risk.

The purpose of the present study was to assess relationships between age at menarche, non-contact ACL injury incidence, and anterior knee laxity in a sample of female collegiate athletes. We tested two related hypotheses. The first was that athletes with previous non-contact ACL injuries would have significantly earlier age at menarche than uninjured athletes. The second was that greater anterior knee laxity would be correlated with time since menarche, which we used as a gross indicator of lifetime estrogen exposure. If the hypotheses are supported, it would suggest that earlier age at menarche is an indicator of increased non-contact ACL injury risk, possibly related to estrogen's effects on ligament laxity.

## *METHODS*

An initial sample of 143 female student athletes was recruited through the university's Athletics Department at preseason physical exams between 2013 and 2015. Study procedures were approved by the local Institutional Review Board, and participants provided informed consent prior to data collection. Athletes under 18 years of age were ineligible due to logistical challenges to obtaining parental consent. Participants were also excluded for premature menarche (age at menarche < 10 y: abnormally early menarche is typically associated with other developmental sequelae likely to confound the study's primary outcomes[36]) or for medical conditions that directly, or indirectly due to treatment, affected their menstrual periods (anemia, Von Willebrand disease, polycystic ovarian syndrome, ovarian hyperstimulation syndrome, and endometriosis). We did not exclude participants for exercise-related functional hypothalamic amenorrhea, since this is very common in the female athlete population, and should thus be included in analysis of the influence of athlete menstrual characteristics on ACL injury risk.

Each participant's birthdate and varsity sports played were recorded. We measured height using a stadiometer, sitting height using the stadiometer and a stool of known height, and body mass using a clinical scale. Subischial leg length was calculated as: (height – sitting height); and body mass index (BMI) was calculated as: (body mass·height$^{-2}$). Subischial leg length and BMI were included as measures of body size and body composition in the analysis of injury risk factors.

### Injury History

Each participant completed an ACL injury questionnaire (self-report of physician's diagnosis and self-report of surgical repair). For each injury reported, the participant was asked to provide date; side; sport or activity engaged in at time of injury; contact or non-contact injury; level of competition; and surgical/non-surgical treatment details.

### Menstrual History

An in-person questionnaire assessed current cycle characteristics, menstrual history, and use of birth control. Two questions focused on age at menarche: "How old were you when you had your first menstrual period?"; and "What was the date of your first menstrual period?" To obtain the most accurate answers, participants were coached by a female co-investigator or research assistant. A guide to typical ages in specific grades in school was also provided as a memory aid. Similar in-person methods have been shown to be moderately-to-highly reliable over recall intervals up to 9 years.[37-39] For analysis, age at menarche was recorded to the most accurate level recalled (month or day). Where only year was recalled (28 of 134 participants), the data were interval censored to reduce recall error by adding 0.5 y to recalled age.[40]

Other characteristics related to menstrual cycle phase and hormonal birth control were recorded, since these factors can affect ligament laxity. Data collected included date of start of last menses, typical cycle length, regularity of monthly cycles (always, sometimes, never), and number of times three or more periods had been missed consecutively. Where participants reported cycle irregularity or missing three or more consecutive periods, they were asked to report any diagnosis of related medical conditions. In addition to reported diagnoses, questionnaire responses were used to identify participants with premature age at menarche (<10 y), primary amenorrhea (age at menarche ≥15 y), secondary amenorrhea (missed ≥3 consecutive periods post-menarcheally), and oligomenorrhea (<9 menstrual periods in a year, estimated using typical cycle length).[36,41] Current and typical cycle length data were used to estimate number of cycles experienced since menarche and current percent of cycle during the arthrometry exam. Information on birth control use was assessed, including current and past usage status, type and brand name used, and ages of onset and termination (if applicable) of use.

## Sports Participation History and Injury Risk Exposure Time

Sports participation data were used with menstrual history details and injury history to quantify time of sports injury risk exposure. Each participant provided details about the age at which she started participating in competitive organized sports. We subtracted age at starting organized sports from current age to calculate total sports injury exposure time. We also used age at menarche to determine whether each athlete began playing organized sports prior to menarche and, if so, by how many years. This information was used to calculate post-menarcheal injury risk exposure time, which we operationally defined as *post-menarcheal years engaged in organized sports without injury*. This value was calculated as follows, depending on participant characteristics:

1) Injured—began playing organized sports pre-menarcheally:
   post-menarcheal injury risk exposure time = age at injury - age at menarche.
2) Injured—began playing organized sports post-menarcheally:
   post-menarcheal injury risk exposure time = age at injury – age at starting organized sports.
3) Uninjured—began playing organized sports pre-menarcheally:
   post-menarcheal injury risk exposure time = current age – age at menarche;
4) Uninjured—began playing organized sports post-menarcheally:
   post-menarcheal injury risk exposure time = current age – age at starting organized sports.

## Arthrometry

Arthrometry exams were performed by two orthopaedic surgery residents who were available for one summer of a research year between postgraduate years one and two. Following that first summer, those two residents began clinical rotations and were no longer available to perform arthrometry exams. Because of the residents' clinical obligations, arthrometry testing was discontinued after this first summer in the interest of minimizing inter-observer error. Arthrometry data are therefore available for only a subset of athletes (N=57). Because laxity data were taken only from uninjured knees, one athlete with bilateral injuries was excluded; a second declined to participate (but her non-arthrometry data were still included in other analyses). This left N=8 injured and N=47 uninjured participants included in the arthrometry analysis. An analog KT-1000™ Knee Ligament Arthrometer (MEDMetric, San Diego, CA) was used to measure passive anterior displacement (PAD) when loaded with ~90 N of anterior force.[42] Within injured participants three trials of each test were performed on the uninjured knee only, and results were averaged across trials for analysis. For uninjured participants, three trials of each measurement were taken bilaterally, and were averaged across trials and across sides for analysis.

## Statistical Analysis

Statistical analysis was performed in SAS 9.4 (Cary, NC) with significance set to $\alpha$=0.05. The study used a convenience sample with no *a priori* statistical power calculations. Descriptive statistics were obtained for sample characteristics, and Pearson correlation coefficients were calculated for the relationships between each variable and age at menarche. Differences between injured and uninjured athletes were analyzed using independent samples t-tests, with effect size estimation using Hedge's $g$[43,44] and common language effect size (CLES).[44,45]

Binomial logistic regression was used to test for the univariate effect of age at menarche on the probability of ACL injury. Covariates were then added to the model to test for their effects, including BMI and subischial leg length, menstrual irregularities (any/none), years of birth control use, and injury risk exposure time. Odds ratios (OR) were calculated for each predictor in this final model. A sensitivity analysis was run including only those athletes playing sports where at least one ACL injury was recorded, to control for potential sport-specific risk effects. The results of this sensitivity analysis were consistent with the results obtained in the analysis of the full sample (i.e., there was no sport-specific influence on the effect of age at menarche), and thus we report only the full sample's results below.

Relationships between PAD, age at menarche, time since menarche, and estimated number of cycles were analyzed using linear mixed models, testing for the interaction of ACL injury status with each menarche-related variable. Where interactions were significant, post hoc univariate linear regressions were run within each injury status group to determine the slopes of PAD vs. menarche-related variables. Secondary linear regression analyses were run to test for covariate effects of observer (the KT-1000 has a moderate degree of inter-observer error[46,47]), current percent of the menstrual cycle, and years of birth control use.

## *RESULTS*

Of the 143 student athletes initially recruited, one participant (with no history of ACL injury) was excluded for premature menarche. Eight participants were excluded for medical conditions related to menstruation (one of whom also reported a prior ACL injury). This resulted in a total sample of N=134 female athletes included for analysis.

### Injury History

Fourteen athletes (10.4%) reported ≥1 ACL injury, all non-contact. Mean age at injury was 17.1±2.6 y (range: 14.0-21.4 y), and all injuries occurred post-menarche (mean years post-menarche=4.5±2.6 y; range: 1.2-8.2 y). Injured athletes' primary sports at the time of data collection (see Table 1) were basketball (5 injuries), soccer (5), cross country/track and field (2), softball (1), and tennis (1). No volleyball, swimming and diving, or cheer/dance athletes reported injuries. Four injured athletes reported secondary injuries, three to the previously injured knee, and one to the contralateral knee.

| **Sport** | **Injured (N)** | **Uninjured (N)** | **Total (N)** | **Total (%)** | **Injury Rate (%)** |
|---|---|---|---|---|---|
| Basketball | 5 | 9 | 14 | 10.4% | 35.7% |
| Cheer and Dance | 0 | 13 | 13 | 9.7% | 0.0% |
| Cross Country/Track and Field | 2 | 25 | 27 | 20.1% | 7.4% |
| Soccer | 5 | 29 | 34 | 25.4% | 14.7% |
| Softball | 1 | 11 | 12 | 9.0% | 8.3% |
| Swimming and Diving | 0 | 21 | 21 | 15.7% | 0.0% |
| Tennis | 1 | 4 | 5 | 3.7% | 20.0% |
| Volleyball | 0 | 8 | 8 | 6.0% | 0.0% |
| **Total** | **14** | **120** | **134** | **100.0%** | **10.4%** |

**Table 1. Primary sports played in injured and uninjured cohorts**

### Menstrual/Birth Control History and Anthropometrics

Descriptive statistics for sample characteristics and correlations with age at menarche are in Table 2, along with comparisons between injured and uninjured groups. Mean age at menarche in the full sample was 13.3±1.4 y, and neither current age, nor any of the anthropometric variables, were significantly correlated with age at menarche (for each, $|r|\leq 0.12$, $P\geq 0.16$). Among injured participants, mean age at menarche was 12.6±1.3 y (range: 10.0-14.8 y) versus 13.4±1.4 y (range:

10.2-17.3 y) in uninjured participants (*P*=0.05; *g*=0.57; CLES=72%; see Fig. 1). Injured athletes were also significantly heavier than uninjured athletes (*P*=0.02; *g*=1.02; CLES=85%). None of the other differences reached statistical significance, although BMI was ~15% higher in the injured group (*P*=0.06; *g*=0.95; CLES=83%).

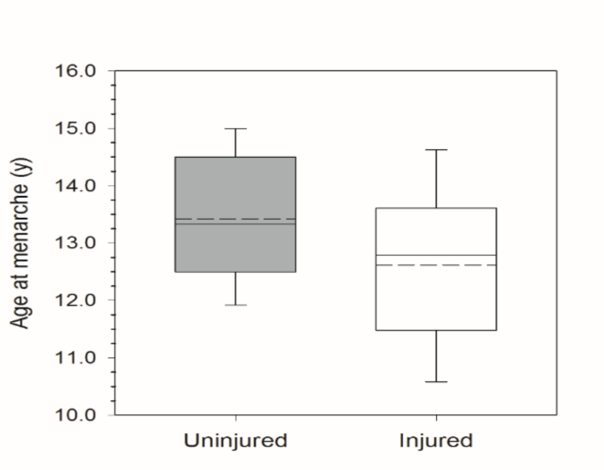

**FIGURE 1. Age at menarche in injured and uninjured athletes (*P*=0.05; *g*=0.57; CLES=72%).**

See Fig. 2 for frequencies of menstrual irregularities and birth control use in injured and uninjured athletes. Frequencies of menstrual irregularities did not differ between the two groups (*P*=0.87). Roughly equal proportions (half) of injured and uninjured participants currently or previously used birth control (respectively: 7 of 14, 50%; 62 of 120, 52%; *P*=0.79), and years of use did not differ between these injured and uninjured participants (2.0±1.6 vs. 2.0±1.3 y, respectively; *P*=0.99; *g*=0.00; CLES=50%).

| Variable | Full sample (N = 134) | | | | Injured (N = 14) | | | Uninjured (N = 120) | | | T-test[b] | Hedge's *g*[c] | CLES[d] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | ± | SD | Pearson's *r*[a] | Mean | ± | SD | Mean | ± | SD | *P* | | |
| **Age (y)** | 19.4 | ± | 1.2 | 0.04 | 19.9 | ± | 1.5 | 19.4 | ± | 1.1 | 0.21 | 0.43 | 67% |
| **Age at menarche (y)** | 13.3 | ± | 1.4 | --- | 12.6 | ± | 1.3 | 13.4 | ± | 1.4 | 0.05 | 0.57 | 72% |
| **Height (cm)** | 167.2 | ± | 7.3 | 0.01 | 170.9 | ± | 7.1 | 167.1 | ± | 5.8 | 0.08 | 0.64 | 74% |
| **Sitting height (cm)** | 88.1 | ± | 3.5 | -0.05 | 89.5 | ± | 3.3 | 87.9 | ± | 3.5 | 0.11 | 0.46 | 68% |
| **Subischial leg length (cm)** | 79.1 | ± | 6.3 | 0.03 | 81.4 | ± | 6.5 | 79.2 | ± | 5.0 | 0.25 | 0.42 | 66% |
| **Body mass (kg)** | 64.4 | ± | 3.5 | -0.12 | 75.3 | ± | 16.7 | 63.1 | ± | 11.3 | 0.02 | 1.02 | 85% |
| **BMI (kg · m$^{-2}$)** | 23.0 | ± | 4.0 | -0.12 | 25.9 | ± | 6.0 | 22.5 | ± | 3.2 | 0.06 | 0.95 | 83% |
| **a.** | Correlations between each variable and age at menarche. For each, *P*≥0.16. | | | | | | | | | | | | |
| **b.** | *P*-values for independent samples t-tests comparing injured and uninjured participants. | | | | | | | | | | | | |
| **c.** | Hedge's *g*: effect size for difference between means, adjusted for standard deviations and unbalanced sample sizes. | | | | | | | | | | | | |
| **d.** | Common language effect size (CLES): probability that for a randomly selected pair of individuals, one injured and one uninjured, the value for the injured individual is higher (or, in the case of age at menarche, lower) than for the uninjured individual. Chance = 50%. We used McGraw and Wong's (1992) weighting for unequal sample sizes in calculating CLES. | | | | | | | | | | | | |

**Table 2. Sample Characteristics**

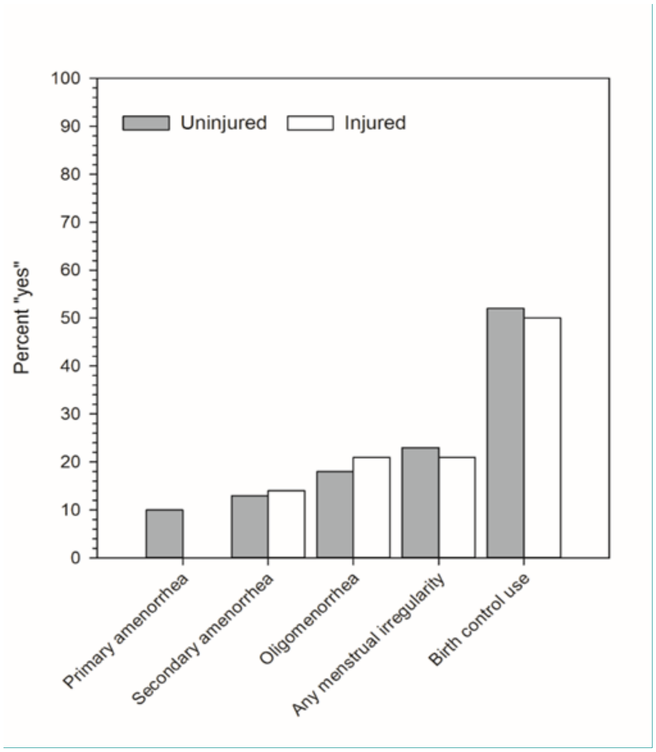

**FIGURE 2. Frequencies of participants in uninjured and injured subgroups exhibiting primary amenorrhea, secondary amenorrhea, oligomenorrhea, or any menstrual irregularity, as well as current or past hormonal birth control use. Frequencies did not differ significantly between groups for any variable (Fisher's exact tests; for each, P≥0.36), and were consistent with previous research in adolescent female athletes.[48] Mean age at menarche among birth control users was 13.5±1.3 y, versus 13.2±1.5 y in participants who had never used birth control (P=0.15; g=0.21; CLES=58%).**

## Sports Participation History and Exposure to Risk

Mean years playing competitive, organized sports was 11.1±3.7 y. Average starting age was 7.9±3.8 y, with 90% of all participants playing sports prior to menarche (90% of uninjured vs. 93% of injured, *P*=0.71), and mean duration of pre-menarche sports participation of 5.5±4.2 y. Age at menarche was not correlated with years of sports participation (*r*=0.12, *P*=0.17) or age at the start of participation (*r*=-0.09, *P*=0.28). Mean age at menarche, however, was later in the 90% of participants who began playing sports pre-menarche (13.4±1.4 y), versus those who began post-menarche (12.5±1.5 y; *P*=0.06; *g*=1.00; CLES=74%). Total years playing competitive, organized sports did not differ between injured and uninjured participants (10.7±3.2 vs. 11.1±3.7, respectively; *P*=0.64; *g*=0.11; CLES=54%), and neither did age at start of sports participation (8.7±3.3 vs. 7.8±3.9; *P*=0.32; *g*=0.27; CLES=61%). Mean post-menarcheal injury risk exposure time for all participants was 5.6±1.9 y, and was 1.5 y longer in uninjured participants (uninjured: 5.7±1.7 y [range: 1.2-8.2 y]; injured: 4.2±2.7 y [range: 0.2-10.4 y]; *P*=0.07; *g*=0.79; CLES=79%; see Fig. 3).

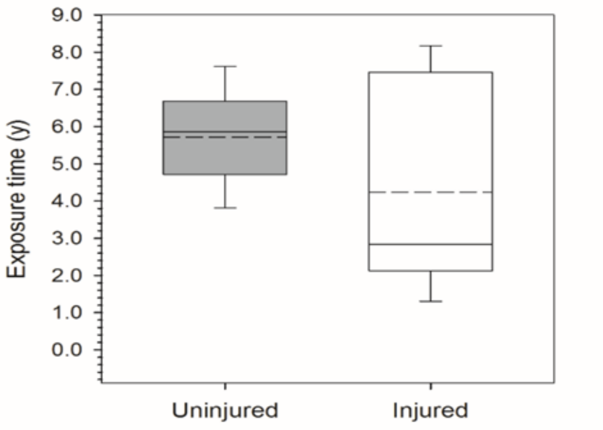

**FIGURE 3. Post-menarcheal sports exposure time in injured and uninjured athletes (*P*=0.07; *g*=0.79; CLES=79%). Solid lines represent the medians, dashed lines represent the means.**

## ACL Injury Risk

Binomial logistic regression found a significant, negative effect of age at menarche on ACL injury risk ($X^2$=4.37; *P*=0.04; *b*=-0.45±0.22), with an OR of 0.64 (95% CI: 0.41-0.99). After adding covariates, the overall model (see Fig. 4 for OR) remained statistically significant ($X^2$=30.04; *P*<0.01). Significant predictors of ACL injury risk were post-menarcheal injury risk exposure time (Wald $X^2$=12.38; *P*<0.01; *b*=-0.91±0.26; OR=0.40; 95% CI: 0.24-0.67), BMI (Wald $X^2$=9.05; *P*<0.01; *b*=0.26±0.09; OR=1.30; 95% CI: 1.09-1.55), and age at menarche (Wald $X^2$=7.43; *P*<0.01; *b*=-1.02±0.37; OR=0.36; 95% CI: 0.17-0.75). Risk was not significantly related to leg length, years of birth control use, or menstrual irregularities (for each, *P*≥0.83).

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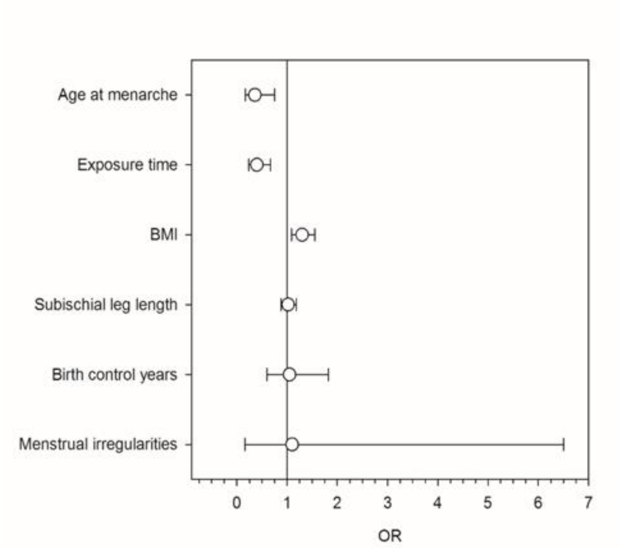

**FIGURE 4. Odds ratios (open circles) with 95% confidence intervals (whiskers) for variables related to ACL injury risk. The solid vertical line represents an OR of 1.00.**

### Anterior Knee Laxity

There were no significant effects of observer (P≥0.27), percent of cycle (P≥0.10), or years of birth control use (P≥0.60) on PAD. Therefore, only the results of univariate analyses of laxity are presented. Injured and uninjured athletes did not differ significantly for PAD (5.8±2.3 mm vs. 5.7±2.0 mm; *P*=0.84; *g*=0.05; CLES=52%), nor was the interaction between injury status and age at menarche significant (*P*=0.17). After removing the interaction term, neither main effect was significant (injury *P*=0.95; age at menarche *P*=0.16). There were, however, significant interactions between injury status and time since menarche (*P*=0.01), and between injury status and estimated number of cycles (*P*=0.03). In both cases, regression slopes for PAD vs. exposure measures were statistically significant in injured, but not uninjured, athletes (Fig. 5).

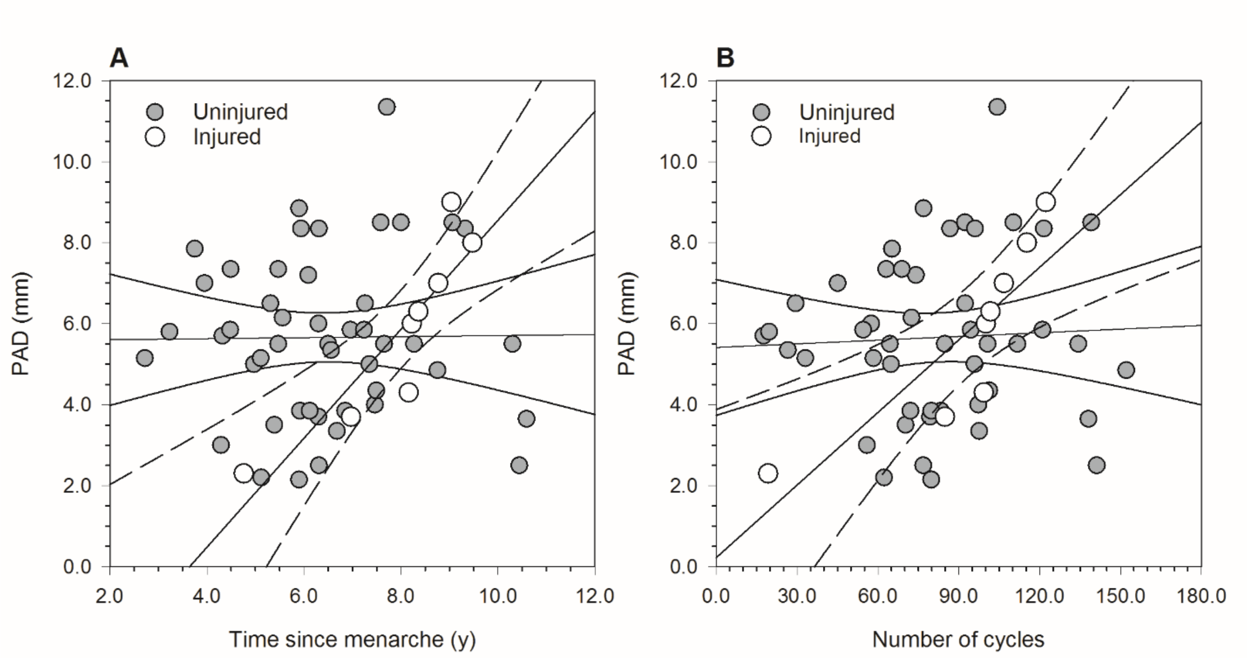

**FIGURE 5. Linear regression results for laxity measures vs. measures of estrogen exposure. Gray circles represent uninjured athletes; white circles represent injured athletes. Solid gray lines (slope) with solid confidence intervals (95% CI of the slope) are for uninjured athletes. Solid black lines (slope) with dashed confidence intervals (95% CI of the slope) are for injured athletes. Regression statistics are as follows: A. PAD vs. time since menarche. Injured: $r^2$=0.79, *b*=1.35±0.28, *P*<0.01; Uninjured: $r^2$<0.01, *b*=0.01±0.17, *P*=0.94. B. PAD vs. number of cycles. Injured: $r^2$=0.72, *b*=0.060±0.015, *P*<0.01; Uninjured: $r^2$<0.01, *b*=0.003±0.009; *P*=0.75.**

## *DISCUSSION*

This study found that earlier age at menarche was associated with a higher probability of non-contact ACL injury risk in female collegiate athletes. Furthermore, among athletes who reported previous ACL injuries, greater anterior knee laxity was related to longer time since menarche, and a greater number of estimated menstrual cycles experienced. These relationships were absent in uninjured athletes. Together, these results suggest that earlier menarche may be an additional, useful screening tool for identifying young females at higher risk for ACL injury.[49]

In terms of injury probability, there was a 72% chance that an injured athlete had an earlier age at menarche than an uninjured athlete, and the odds of an ACL injury increased by 56% for every year of earlier age at menarche. When the significant covariates post-menarcheal injury risk, exposure time, and BMI were included in the model, the odds of injury were nearly threefold higher for each year of earlier age at menarche. Of the 15 athletes reporting ≥1 injury in our study, the three reporting multiple injuries all had very early ages at menarche of 10.0, 11.2, and 11.5 y. These ages were all below the 10th percentile for the sample, further supporting the effect of earlier menarche on injury risk.

One possible explanation for the observed results is that earlier, and thus potentially longer, exposure to post-pubertal ACL injury risk is, by default, a correlate of earlier menarche. Riskier knee biomechanics characteristic of post-pubertal females (reduced flexion; greater peak valgus angles and moments) emerge during puberty, and thus age at menarche may serve in part as a simple proxy for the timing of these neuromuscular developments.[11-15,20,50,51] The observed effect of earlier menarche could therefore be nothing more than an artifact of longer exposure to riskier post-pubertal movement patterns: for a given age, athletes who entered the post-pubertal period of higher risk earlier would have naturally accrued greater cumulative years of injury risk.

In this sample, however, participants *without* a previous ACL injury had been playing injury-free post-menarcheal organized sports 1.5 years *longer* than the injured participants' average time to ACL injury post-menarche. The logistic regression results show that *shorter* exposure time is related to greater odds of injury, reflecting the relatively short average post-menarcheal time to injury among injured participants. Simply spending more time in the post-pubertal high-risk period does not appear to explain the observed relationship between earlier age at menarche and higher ACL injury incidence.

Alternatively, earlier menarche may be related to an increased tendency to exhibit the risky biomechanical profiles associated with females more generally. Although we did not test this hypothesis specifically, some of our results may point to potential avenues of related future research. Even if puberty is associated with a shift toward riskier knee biomechanics in females on average, there is considerable inter-individual variability, some of which may be related to variation in pubertal timing and its effects on body size and shape.[21] Some of our results hint at covariation in age at menarche, variation in body size and shape, and ACL injury risk. For example, we found a significant effect of BMI on injury status, the OR for which (1.30) indicates that for every 1 $\text{kg}\cdot\text{m}^{-2}$ increase in BMI, the odds of ACL injury rises by 30%. Injured participants were heavier than uninjured participants, and exhibited a strong trend toward higher BMI and greater height (although not statistically significant, $P \leq 0.10$, and CLES ≥74% indicate large effect sizes). Greater height, body mass, and BMI increase joint loads, potentially elevating injury risk through greater absolute ACL loading during activity. Greater height may also indicate a higher center of gravity, and thus a longer moment arm for gravity to destabilize the body. When paired with higher BMI, more superiorly distributed mass results in a greater moment of inertia and higher angular momentum in the upper body, making it more difficult to control. The neuromuscular demands of upper body stabilization can have consequences throughout the kinetic chain, including at the knee, where injury risk may thus be elevated.[52,53]

Greater anterior knee laxity associated with earlier menarche may also contribute to mechanical risk and the injury pattern observed in these athletes. Surges in circulating estrogen during the menstrual cycle are related to increased ligamentous laxity and concomitant impairment of thigh muscle function related to knee stability and ACL protection.[29,33,54,55] These factors are associated with increased ACL strain and injury risk,[24-26] and, as with neuromuscular risk factors, greater laxity in females vs. males emerges during puberty.[17,26] Because estrogen peaks during a single menstrual cycle can have effects on laxity,[29] athletes with earlier menarche could also exhibit greater laxity due to cumulative effects of experiencing more cycle peaks compared to peers with later menarche.

While we expected that earlier menarche would be associated with greater laxity, this relationship was only observed within injured individuals in the present study. Given the small sample of injured athletes, these results are preliminary, and it remains largely beyond the capacity of this dataset to explain the observed discrepancy between injured and uninjured groups. However, there is evidence for heritable variation in estrogen receptor density in female ACL tissue, raising the intriguing possibility that interactions between age at menarche, menstrual estrogen cycling, and ACL estrogen sensitivity together contribute to injury risk.[56,57] Future prospective studies are needed to more effectively examine relationships between age at menarche, menstrual cycle phase, ligament estrogen receptors, and ACL injuries.[58]

Implicit in our hypotheses are the assumptions that sex differences in ACL injury risk, whether due to knee mechanics or to ligament laxity, are sequelae of elevated estrogen exposure. This is an important assumption, since we did not measure estrogen levels and instead use age at menarche as a proxy for the onset of estrogen exposure and relative lifetime estrogen exposure. This assumption is not without pitfalls, and without precisely timed serial hormone assays, we cannot determine actual estrogen exposure levels or their contributions to injury risk in this sample. There are, however, reasons to think that, in general, earlier age at menarche is associated with greater lifetime exposure to estrogen. Elevated risk due to increased estrogen exposure may begin shortly after menarche, despite a slow, multi-year process of developing full menstrual regularity. Even irregular cycles, which are the norm shortly after menarche, still tend to be ovulatory and accompanied by estrogen peaks.[59] Studies have also shown no relationship between age at menarche and a tendency for irregular or anovulatory cycles, or have instead shown greater irregularity to be associated with later menarche.[60,61] Female athletes exhibit higher rates of menstrual disturbances during adolescence compared to non-athlete peers, but evidence suggests these are more common in female athletes with later menarche.[62,63] Together, the data suggest that female athletes with earlier menarche likely begin experiencing ovulatory estrogen peaks at younger ages, and perhaps more frequently than their peers with later menarche. If there are cumulative effects of prolonged estrogen exposure on ligament laxity, this too would in theory put females with earlier menarche at higher risk for ACL injury.

Limitations to this study include potential menarche recall discrepancies, arthrometer observer effects, lack of hormone assays, and a relatively small sample size for injured athletes. Age at menarche and menstrual cycle details were assessed by recall questionnaire, which incorporates some error. Error was minimized by in-person questionnaires and post hoc centering of integer age data.[39] Since two residents performed the arthrometry exams, inter-observer error associated with the KT-1000 could also affect the results; however, sensitivity analysis found no effect of observer on laxity measurements. Our follow-up research will use alternative arthrometry methods (Telos™ stress radiography) to assess laxity. Hormone levels were also not collected at the time of the exam, nor were historical/longitudinal hormone data available for these participants. The reliance on recall of menstrual cycle characteristics necessarily introduces error into analyses incorporating estimated number of cycles and rates of menstrual irregularity.[64] Finally, the small sample of injured athletes may have constrained the statistical power of some analyses.

## *CONCLUSIONS*

Puberty is commonly associated with elevated ACL injury risk in females.[11] Despite considerable observed inter-individual variability in pubertal timing, there is little research on the effect of this variation on injury incidence. The present study provides evidence for an effect of pubertal variability, in the form of earlier age at menarche, on ACL injury risk, potentially through effects on ligament laxity. Because age at menarche is an easily obtained data point, it can be used to help athletes, parents, coaches, trainers, therapists, and physicians coordinate optimal training programs to protect those young female athletes who may have elevated injury risk due to developmental timing.

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