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# Quadriceps muscle volume positively contributes to ACL volume

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## Abstract

Females have smaller anterior cruciate ligaments (ACLs) than males and smaller ACLs have been associated with a greater risk of ACL injury. Overall body dimensions do not adequately explain these sex differences. This study examined the extent to which quadriceps muscle volume ($VOL_{QUAD}$) positively predicts ACL volume ($VOL_{ACL}$) once sex and other body dimensions were accounted for. Physically active males ($N = 10$) and females ($N = 10$) were measured for height, weight, and body mass index (BMI). Three-Tesla magnetic resonance images of their dominant and nondominant thigh and knee were then obtained to measure $VOL_{ACL}$, quadriceps, and hamstring muscle volumes, femoral notch width, and femoral notch width index. Separate three-step regressions estimated associations between $VOL_{QUAD}$ and $VOL_{ACL}$ (third step), after controlling for sex (first step) and one body dimension (second step). When controlling for sex and sex plus BMI, $VOL_{HAM}$, notch width, or notch width index, $VOL_{QUAD}$ consistently exhibited a positive association with $VOL_{ACL}$ in the dominant leg, nondominant leg, and leg-averaged models ($p < 0.05$). Findings were inconsistent when controlling for sex and height ($p = 0.038–0.102$). Once $VOL_{QUAD}$ was included, only notch width and notch width index retained a statistically significant individual association with $VOL_{ACL}$ ($p < 0.01$). *Statement of Clinical Significance*: The positive association between $VOL_{QUAD}$ and $VOL_{ACL}$ suggests ACL size may in part be modifiable. Future studies are needed to determine the extent to which an appropriate training stimulus (focused on optimizing overall lower extremity muscle mass development) can positively impact ACL size and structure in young females.

**KEYWORDS**
ACL morphology, anatomical risk factors, anterior cruciate ligament, muscle mass

## 1 | INTRODUCTION

Despite the development of anterior cruciate ligament (ACL) prevention programs more than 20 years ago, the incidence of ACL injury has continued to rise.[1] The number of athletes that must be treated to prevent one ACL injury from occurring (89–120) also remains high.[2,3] This is of particular concern for adolescent and young adult females who are more likely than similarly trained males to suffer both primary[4] and secondary ACL injuries.[5] These young females are often not able to return to their prior competitive level of sport[6] and more than 30% are at substantial risk of developing osteoarthritis within 10 years of the initial injury.[7] Prevention efforts have largely focused on neuromuscular training to modify "high-risk" biomechanical movement patterns and subsequently reduce external loads placed on the ACL.[8] Anatomical risk factors are often considered "non-modifiable" and have been largely ignored in ACL injury prevention efforts. However, what causes these anatomical risk factors to develop and whether they are truly nonmodifiable, is not well understood.

ACL size is an anatomical factor associated with ACL injury risk. Whether measured as cross-sectional area (CSA) or volume, ACL size varies widely within and between sex,[9] and on average is substantially smaller in females compared to males (CSA = 17%–39% smaller; volume =10%–35% smaller).[9] Smaller ACLs have also been observed in the contralateral knee of those who have torn their ACL compared to healthy matched controls.[10–12] Smaller ACLs have been associated with less linear stiffness,[13,14] lower load at failure,[13,14] and greater anterior knee laxity.[15] In turn, greater anterior knee laxity is associated with a greater risk of ACL injury, particularly in females.[16,17] Understanding the factors that contribute to interindividual and intersex variability in ACL size, and subsequently lead to a smaller and weaker ACL in females, may lead to novel prevention strategies aimed at improving the resiliency of the ACL and reducing injury risk.

Sex differences in ACL size emerge about the same time that the risk of ACL injury rises disproportionately in females compared to males (age 13–16 years).[1] ACL CSA increases linearly up to age 10 in both sexes,[18,19] with ~20% smaller values in females reported as early as 11–14 years of age.[18] Smaller ACLs are clearly present in females by 15–18 years of age (~25% smaller)[18,20] and continue into adulthood (18%–34% smaller).[21–24] These sex differences are not explained by body dimensions alone. Though correlations have been observed between ACL size and various dimensions such as height, weight, body mass index (BMI), and femoral geometry, the extent to which these dimensions explain sex differences in ACL volume or simply act as a surrogate for sex in the analyses is not clear. For example, significant correlations have been reported between height and ACL volume when data from both sexes are pooled.[21,22] However, this association is diminished when data are stratified by sex[20,21] and females still have smaller ACLs than males after accounting for height.[18,25] Similarly, females still have smaller ACLs once body mass[20,21] and BMI[21,24] are accounted for. Femoral notch geometry also does not adequately explain sex differences in ACL size.[23] In studies where females and males had similar notch width (NW) or notch width index (NWI), females still had 26%–34% smaller ACLs.[20,21] In other studies where females had both smaller ACL sizes and NWs than males,[20,24] ACL volume did not vary in proportion to femoral notch dimensions,[20] and females still had 20% smaller ACL volume once accounting for the femoral NW.[24] Thus, whole-body or knee joint dimensions do not fully explain the variability in ACL size when controlling for sex.

Ligaments are dynamic tissues that are known to respond to the loading stress placed on the joint. As such, less relative thigh muscle mass may be a relevant factor driving a female's smaller ACL volume. Like ACL volume,[18,19] sex differences in muscle mass develop after age 10, and muscle mass plateaus in females by 13–14 years of age while it continues to increase in males.[26] Though there is good evidence that muscle mass is strongly coupled with bone mass and quality (i.e., density) in young females,[27,28] studies examining associations between thigh muscle mass and ligament size are limited. Chandrashekar et al.[21] reported lean body mass was a positive predictor of ACL volume when data from both sexes were pooled, but this association diminished once data were stratified by sex. However, lean mass was estimated using anthropomorphic data, not measured directly.[21] In high school-aged male and female basketball players who differed in height, weight, and percent body fat (lean body mass), female ACLs were 26.2% ($p < 0.0001$) smaller when compared on absolute CSA, 14.3% smaller ($p < 0.003$), when compared on CSA, normalized to body weight, but only 3.6% ($p = 0.9$) smaller when compared on CSA, normalized to lean body mass (derived from percent body fat calculations via skinfold calipers).[20] Though these findings suggest muscle mass may be a stronger determinant of ACL size than other body dimensions, direct measures of muscle morphology are lacking. Should muscle morphology uniquely contribute to interindividual and intersex differences in ACL size, this would hold promise that ACL size and resiliency may be in part be modifiable through resistance training.

The purpose of this study was to determine the extent to which thigh muscle mass, as measured by quadriceps muscle volume (the primary extensor of the knee joint and ACL antagonist) is positively associated with ACL volume once accounting for sex and each of the other body dimensions (height, weight, BMI, hamstring muscle volume, femoral notch geometry). Though both ACL volume and CSA have been correlated with body dimensions, we chose to examine ACL volume for this correlational study given reports that ACL volume may represent a more precise measure of ACL size, thus may better clarify relationships between sex and body dimensions.[24] ACL volume has also been examined more often relative to ACL injury risk.[10–12] We hypothesized that once sex and each of the other body dimensions is accounted for, quadriceps volume would be a significant contributor to ACL volume.

## 2 | METHODS

This is a retrospective cohort study (Level 3 evidence) of 10 healthy males (23.2 ± 3.4 years) and 10 healthy females (22.8 ± 3.0 years) who reported being physically active at least three times per week for 30 min per day and a score of 3 or higher on the Marx Activity Rating Scale (males = 11.6 ± 3.1, range = 7–16; females = 7.7 ± 2.4, range = 4–12). Healthy was defined as having no current orthopedic injury or prior history of ligament injury or surgery to either limb. Seventeen of 20 participants were right leg dominant (defined as the leg one would use to kick a soccer ball). All participants read and signed a University IRB-approved informed consent before participation.

All subjects were measured for height, mass, and their BMI calculated. They then underwent imaging of their dominant and nondominant thigh and knee using a 3-T magnetic resonance image system (Trio; Siemens) using previously published techniques.[29,30] Knee scans were acquired first with a 15-channel knee coil (Siemens). T2-weighted, multiplanar scans (repetition [TR] = 1,300 ms, excitation time [TE] = 39 ms; Flip angle [FA] = 160°; field of view [FOV] = 150 × 150 mm; voxel size 0.5 × 0.5 × 0.5 mm) were acquired for ACL volume and T1-weighted, multi-planar scans (TR = 1,200 ms, TE = 33 ms; FOV = 160 × 160 mm; voxel size 0.5 × 0.5 × 0.6 mm) were acquired for femoral notch dimensions. A single investigator, blinded to participant sex, calculated ACL volume using ITK-SNAP software (http://www.itksnap.org/pmwiki/pmwiki.php) and using the methods of Chaudhari et al.[10] The ACL was manually contoured in each image slice using a digital tablet (Wacom DTK1300; Wacom Co.) and slices were spatially summed to acquire volume. Measurement reliability and precision have been previously reported ($ICC_{3,1} \pm SEM = 0.97 \pm 36.1\ mm^3$).[24]

Femoral NW and NWI were measured with Medical Image Processing, Analysis, and Visualization software (http://mipav.cit.nih.gov) using methods reported by Stein et al.[31] The axial image was chosen based on the sagittal image that had the clearest view of the Blumensaat line and from the frontal image that identified the beginning of the Blumensaat line. From this axial image, a line was drawn perpendicular from the articular surface line (line tangent to the medial and the lateral femoral condyle) to the most anterior portion of the notch to determine notch depth. NW was measured as the distance of the line drawn parallel to the articular surface line at two-thirds of the notch depth. NWI was measured as the ratio of the NW to the bicondylar femoral width also measured at 2/3 of the notch depth. A single examiner with previously reported intratester reliability and precision ($ICC_{3,1} \pm SEM = 0.99 \pm 0.2$ mm; equivalent to 1.1% of mean femoral NW) obtained all measures.[12]

Thigh muscle imaging was then performed after lying supine for at least 10 min to control for any fluid shifts in volume measurements. Body coils were placed anteriorly and posteriorly, and T1-weighted fat-suppressed (SPAIR) frontal MRI scans from the hip joint to the knee joint were acquired (1.0-mm slice thickness, 3.0 × 3.0-mm in-plane resolution, 256 slices, 480 × 480 FOV, 1,200-ms TR, 33-ms TE, flip angle = PdVar, and 539-Hz/pixel bandwidth. CSAs for each individual muscle of the quadriceps and hamstring muscle groups were outlined by a single examiner in 2.25-cm intervals from the lateral joint line to the hip joint center (Osirix v 5.7.1, Osirix Foundation). Additionally, the most proximal and distal aspects of each muscle were also outlined. CSAs for each interval were then fitted with a cubic spline, plotted against femur length, and volume calculated as the area under the curve using measured and spline data points.[32,33] The individual muscles were then summed to obtain a single quadriceps muscle volume and a single hamstring muscle volume for the dominant limb, the nondominant limb, and an average of the two limbs. The validity of this method has been previously reported,[33,34] and the examiner (Anthony S. Kulas) demonstrated excellent measurement reliability and precision (error < 1% of total volume) in 10 participants on two separate occasions (ICC ± SEMs = 0.98 ± 12.1 $cm^3$ quadriceps, 0.99 ± 5.8 $cm^3$ hamstrings).[29]

## 2.1 | Data analyses

Ordinary least squares regression was used to estimate associations between quad muscle volume ($VOL_{QUAD}$) and ACL volume ($VOL_{ACL}$) while controlling for sex and while controlling for sex plus one of the physiological indices often correlated with $VOL_{ACL}$ (height, mass, BMI, hamstring muscle volume, femoral NW, femoral NWI). Separate regression models were estimated for each physiological covariate due to the study sample size and the high intercorrelations between the physiological indices. On the basis of a sample size of 20 and three predictors in the model, we had 80% power to detect an overall $R^2 > 0.30$, where the partial $R^2$ between $VOL_{QUAD}$ and ACL volume ranged from 0.10 to 0.30 while holding the two other predictors constant (G*Power Version 3.1.9.4). This represents a moderate to large effect and was considered acceptable for establishing a meaningful contribution of $VOL_{QUAD}$. Regression models were built in a three-step hierarchical fashion, in which sex was entered at step-1, one additional physiological covariate was entered at step-2 (except for the model with only sex) and $VOL_{QUAD}$ was entered at step-3. Models were constructed in this fashion to allow for examination of potential changes in the significance of sex and the physiological covariates from step-1 to step-2 as well as changes in adjusted-$R^2$ values when adding $VOL_{QUAD}$ to the model at step-3. Further, squared semipartial correlations were calculated at step-2 and step-3 to estimate the percentage of variance in $VOL_{ACL}$ uniquely accounted for by the physiological covariates and by $VOL_{QUAD}$, respectively; that is, the contribution of each predictor to ACL volume above and beyond what the other variables contribute. All continuous predictor variables were mean-centered to simplify the interpretation of intercepts and regression coefficients. NWI scores were also multiplied by 100 to facilitate the interpretation of coefficient values. Models were estimated separately for dominant, nondominant, and averaged leg values. All analyses were conducted using SPSS v26 and R (https://www.r-project.org/) using the "ppcor" package.[35]

# 3 | RESULTS

Demographic data are presented in Table 1 for descriptive purposes only. Bivariate correlations between the physiological covariate scores calculated from averaged leg composites demonstrate high correlations between ACL volume and all body dimensions examined, as well as moderate to high intercorrelations between the predictor variables (Table 2).

Full model results from step-1 (sex) and step-2 (physiological indices) and from step-3 ($VOL_{QUAD}$) are presented in Tables 3 and 4, respectively. Without $VOL_{QUAD}$ in the model (Table 3), models that controlled only for sex, and for sex plus height, mass, NW, or NWI were all positively and significantly associated with nondominant leg and leg-averaged $VOL_{ACL}$ ($p < 0.05$). Similar results were observed for dominant $VOL_{ACL}$ with all physiological covariates except for height, for which the association failed to reach significance. When

TABLE 1 Subject demographics (mean±sd)

| | All | Female | Male |
|---|---|---|---|
| Age (years) | 23.0 (3.1) | 22.8 (3.0) | 23.2 (3.4) |
| Height (m) | 1.72 (0.11) | 1.64 (0.07) | 1.80 (0.08) |
| Mass (kg) | 72.2 (14.7) | 62.1 (9.3) | 82.3 (12.0) |
| BMI (kg/m$^2$) | 24.3 (3.6) | 23.2 (2.9) | 25.4 (4.0) |
| NW (mm)[a] | 17.3 (2.0) | 16.2 (1.4) | 18.3 (2.0) |
| NWI (ratio*100)[a] | 24.2 (2.0) | 24.5 (1.6) | 23.9 (2.3) |
| $VOL_{HAM}$ (cm$^3$)[a] | 747.5 (237.3) | 562.9 (75.1) | 932.0 (193.8) |
| $VOL_{QUAD}$ (cm$^3$)[a] | 1,999.5 (699.1) | 1,452.9 (250.7) | 2,546.1 (552.4) |
| $VOL_{ACL}$ (mm$^3$)[a] | 1,564.5 (406.8) | 1,333.2 (236.6) | 1,795.8 (417.8) |

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; NW, femoral notch width; NWI, femoral notch width index; $VOL_{ACL}$, ACL volume; $VOL_{HAM}$, hamstring muscle volume; $VOL_{QUAD}$, quadriceps muscle volume.

[a]Values reported represent the average of the left and right limbs.

$VOL_{QUAD}$ was added to the models (Table 4), only NW and NWI retained a statistically significant individual association with $VOL_{ACL}$ ($p < 0.01$). When controlling for BMI, $VOL_{HAM}$, NW or NWI, $VOL_{QUAD}$ was consistently significantly positively associated with $VOL_{ACL}$ in the dominant leg, nondominant leg, and leg-averaged models ($p < 0.05$). Findings were less consistent when controlling for height, and consistently nonsignificant when controlling for total body mass.

On average, step-2 models (Table 3) that included BMI or $VOL_{HAM}$ explained the least amount of variance in $VOL_{ACL}$, and so tended to yield the largest increases in adjusted-$R^2$ once $VOL_{QUAD}$ was added at step-3 (Table 4). These were also the models for which $VOL_{QUAD}$ semipartial correlations were the largest, accounting for 17%–23% of the variance in $VOL_{ACL}$.

## 4 | DISCUSSION

Our primary finding was that $VOL_{QUAD}$ positively contributed to $VOL_{ACL}$ once accounting for sex and other body dimensions previously correlated with $VOL_{ACL}$ (height, weight, BMI, hamstring muscle volume, femoral notch geometry). The contribution of $VOL_{QUAD}$ that was above and beyond what was explained by other variables in the model ranged from 7% to 23%. It is also important to note that once $VOL_{QUAD}$ was included in the models, the contribution of sex and the other body dimensions decreased considerably and were no longer significant contributors to the model. The exception to this was the models containing femoral notch geometry. The only model in which $VOL_{QUAD}$ did not consistently and significantly contribute to $VOL_{ACL}$ was total body mass and height. This is not surprising as muscle volume was strongly correlated to both (Table 2). Still, the semipartial correlation for both mass and height was reduced and no longer significant once $VOL_{QUAD}$ was entered into the model ($p = 0.116–0.550$), and the semipartial correlation for $VOL_{QUAD}$ reached or neared significance when height was controlled for on the nondominant and averaged sides ($p = 0.04–0.06$) (Tables 4 and 5). Though this suggests that the amount of muscle mass may be a stronger contributor to ACL volume than mass or height, futures studies should confirm these findings in a larger cohort. These associations may also explain why studies identifying smaller ACL volume in ACL-injured versus healthy controls, identified that age, height, and BMI had no effect on this relationship, whereas body weight strengthened the relationship between ACL size and injury risk.[10,11]

$VOL_{QUAD}$ was more strongly associated with $VOL_{ACL}$ than was $VOL_{HAM}$. Once accounting for sex, $VOL_{QUAD}$ independently explained 19%–23% of the variance ($p < 0.05$) compared to $VOL_{HAM}$ which explained only 7%–9% of the variance ($p > 0.05$). Moreover, the independent association between $VOL_{QUAD}$ and $VOL_{ACL}$ remained relatively unchanged with and without $VOL_{HAM}$ in the model (Table 5). Because the quadriceps act as an antagonist to the ACL, the stronger relationship between $VOL_{QUAD}$ and $VOL_{ACL}$ may represent positive adaptations to the ACL with loading

TABLE 2 Bivariate correlations ($r$) for the average of the left and right limbs

| | Height | Mass | BMI | $VOL_{HAM}$ | NW | NWI | $VOL_{QUAD}$ |
|---|---|---|---|---|---|---|---|
| $VOL_{ACL}$ | 0.685* | 0.708* | 0.356 | 0.638* | 0.826* | 0.537** | 0.747* |
| Height | | 0.699* | 0.101 | 0.716* | 0.574* | 0.106 | 0.784* |
| Mass | | | 0.780* | 0.853* | 0.495** | 0.017 | 0.830* |
| BMI | | | | 0.559** | 0.167 | −0.100 | 0.467** |
| $VOL_{HAM}$ | | | | | 0.415*** | −0.157 | 0.962* |
| NW | | | | | | 0.687* | 0.569* |
| NWI | | | | | | | −0.010 |

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; NW, femoral notch width; NWI, femoral notch width index; $VOL_{HAM}$, hamstring muscle volume; $VOL_{QUAD}$, quadriceps muscle volume; $VOL_{ACL}$, ACL volume.

*$p < 0.05$.
**$p < 0.01$.
***$p < 0.10$.

**TABLE 3** Regression results and beta weights predicting $VOL_{ACL}$ accounting for sex (Step-1) and each body dimension (Step-2)

| | Intercept | Female | Height | Mass | BMI | $VOL_{HAM}$ | NW | NWI | Quad | $R^2_{Adj}$ | $p_{fit}$ | $R^2_{COV}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nondominant | 1,753.5 | −426.4** | | | | | | | | 0.29 | 0.009 | – |
| | 1,564.3 | −48.0 | 2,279.6* | | | | | | | 0.47 | 0.002 | 0.20 |
| | 1,606.1 | −131.9 | | 14.6* | | | | | | 0.42 | 0.004 | 0.16 |
| | 1,739.6 | −398.6* | | | 12.4 | | | | | 0.26 | 0.031 | 0.01 |
| | 1,595.1 | −109.6 | | | | 0.9 | | | | 0.34 | 0.011 | 0.09 |
| | 1,626.5 | −172.5 | | | | | 129.5** | | | 0.60 | 0.000 | 0.32 |
| | 1,788.5 | −496.4** | | | | | | 125.9** | | 0.69 | 0.000 | 0.40 |
| | 1,536.7 | 7.1 | | | | | | | 0.4* | 0.48 | 0.002 | 0.21 |
| Dominant | 1,838.1 | −498.7** | | | | | | | | 0.30 | 0.007 | – |
| | 1,693.5 | −209.6 | 1,741.8 | | | | | | | 0.36 | 0.009 | 0.09 |
| | 1,655.9 | −134.3 | | 18.0* | | | | | | 0.46 | 0.002 | 0.18 |
| | 1,804.1 | −430.8* | | | 30.3 | | | | | 0.32 | 0.015 | 0.05 |
| | 1,693.9 | −210.4 | | | | 0.8 | | | | 0.34 | 0.012 | 0.07 |
| | 1,681.4 | −185.4 | | | | | 147.8*** | | | 0.67 | 0.000 | 0.37 |
| | 1,876.9 | −576.4** | | | | | | 116.9** | | 0.63 | 0.000 | 0.33 |
| | 1,498.4 | 83.8 | | | | | | | 0.5** | 0.50 | 0.001 | 0.22 |
| Average | 1,795.8 | −462.6** | | | | | | | | 0.30 | 0.007 | – |
| | 1,628.9 | −128.8 | 2,010.7* | | | | | | | 0.42 | 0.004 | 0.14 |
| | 1,631.1 | −133.1 | | 16.3* | | | | | | 0.46 | 0.002 | 0.18 |
| | 1,771.85 | −414.70* | | | 21.4 | | | | | 0.30 | 0.019 | 0.03 |
| | 1,645.48 | −161.97 | | | | 0.8 | | | | 0.35 | 0.009 | 0.08 |
| | 1,645.13 | −161.27 | | | | | 147.7*** | | | 0.68 | 0.000 | 0.37 |
| | 1,837.01 | −545.02** | | | | | | 135.1*** | | 0.72 | 0.000 | 0.41 |
| | 1,546.99 | 35.02 | | | | | | | 0.5* | 0.51 | 0.001 | 0.22 |

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; NW, femoral notch width; NWI, femoral notch width index; $R^2_{adj}$, adjusted $R^2$ for the entire model; $R^2_{COV}$, individual association of the covariate with $VOL_{ACL}$; $VOL_{ACL}$, ACL volume; $VOL_{HAM}$, hamstring muscle volume; $VOL_{QUAD}$, quadriceps muscle volume.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

stress.[36] However, bivariate correlations indicate that $VOL_{HAM}$ was also positively correlated with $VOL_{ACL}$, so it is also possible that there is less error in the measurement of $VOL_{QUAD}$ compared to $VOL_{HAM}$. Research suggests that the hamstring muscles have a higher proportion of intramuscular fat content (i.e., are less dense) than the quadriceps and that intramuscular fat is strongly correlated with BMI.[37] Future studies are needed to determine if both quantity (volume) and quality (density) are relevant factors predicting ACL size.

Once $VOL_{QUAD}$ was added to the model, NW and NWI were the only physical dimensions that remained significant contributors to $VOL_{ACL}$. Though correlations between notch dimensions and ACL size have been previously reported, studies have not found these dimensions to adequately explain sex differences in ACL size.[20,21,23,23,24] This was clearly evident for our femoral NWI results where the relationship between sex and $VOL_{ACL}$ was actually strengthened once femoral NWI was accounted for (see part correlations in Table 5). When adding $VOL_{QUAD}$ on the next step, the association with femoral NWI was retained (and remained relatively unchanged), whereas sex contributed less than 2% of the variance. Conversely, femoral NW substantially reduced the variance explained by sex (from 32% to <4%). This is not surprising as sex differences are commonly observed in femoral NW (an absolute skeletal measure proportional to overall body size) but not NWI (value normalized to skeletal size).[20,21,23,23,24] Despite these associations between sex, femoral NW and NWI, $VOL_{QUAD}$ uniquely contributed to the models for both NW and NWI, explaining an additional 9%–16% of the variance. These findings suggest that though some anatomical factors associated with $VOL_{ACL}$ may be structural and nonmodifiable, there are others that may be modifiable through training.

Animal studies demonstrate that ligaments are dynamic tissues that respond to inactivity as well as exercise training, and can increase in size, strength, and stiffness if the training protocol is sufficient to load the bone–ligament–bone complex and stimulate changes in collagen structure.[38–40] Though positive adaptations in the size and quality of bone and tendon have been observed in response to resistance training in both sexes,[41] human studies of ligament adaptations are scarce. In one study, male weight lifters had 44% greater ACL CSA compared to

**TABLE 4** Regression model predicting $VOL_{ACL}$ after adding $VOL_{QUAD}$ (Step-3)

| | Intercept | Female | Height | Mass | BMI | $VOL_{HAM}$ | NW | NWI | $VOL_{QUAD}$ | *p*-fit | $R^2_{Adj}$ | Unadjusted $\Delta R^2_{Adj}$ | Unadjusted $R^2_{Tot}$ | $R^2_{Quad}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nondominant | 1,478.9 | 122.8 | 1,518.3 | | | | | | 0.28 | 0.002 | 0.53 | 0.06 | 0.60 | 0.08 |
| | 1,526.0 | 28.5 | | 6.3 | | | | | 0.31 | 0.005 | 0.46 | 0.05 | 0.55 | 0.07 |
| | 1,531.7 | 17.1 | | | −9.4 | | | | 0.44* | 0.005 | 0.45 | 0.19 | 0.54 | 0.20 |
| | 1,599.3 | 118.0 | | | | −1.9 | | | 0.93* | 0.002 | 0.53 | 0.19 | 0.60 | 0.19 |
| | 1,492.7 | 95.1 | | | | | 108.7** | | 0.29* | 0.000 | 0.69 | 0.09 | 0.74 | 0.10 |
| | 1,633.0 | −185.1 | | | | | | 110.2*** | 0.29* | 0.000 | 0.79 | 0.09 | 0.82 | 0.10 |
| Dominant | 1,530.4 | 116.7 | 657.4 | | | | | | 0.45* | 0.003 | 0.48 | 0.12 | 0.56 | 0.14 |
| | 1,538.2 | 101.1 | | 9.8 | | | | | 0.36 | 0.002 | 0.51 | 0.05 | 0.59 | 0.07 |
| | 1,559. 6 | 58.3 | | | 10.7 | | | | 0.47* | 0.004 | 0.48 | 0.16 | 0.56 | 0.17 |
| | 1,554.2 | 69.1 | | | | −1.7**** | | | 1.07* | 0.001 | 0.57 | 0.23 | 0.64 | 0.23 |
| | 1,506.2 | 165.4 | | | | | 126.6*** | | 0.35* | 0.000 | 0.77 | 0.10 | 0.81 | 0.10 |
| | 1,629.6 | 81.8 | | | | | | 106.7*** | 0.43** | 0.000 | 0.79 | 0.16 | 0.82 | 0.16 |
| Average | 1,507.4 | 114.2 | 1,077.8 | | | | | | 0.36**** | 0.002 | 0.51 | 0.09 | 0.59 | 0.11 |
| | 1,534.2 | 60.5 | | 8.1 | | | | | 0.33 | 0.002 | 0.51 | 0.05 | 0.58 | 0.07 |
| | 1,547.4 | 34.2 | | | 0.8 | | | | 0.45* | 0.004 | 0.48 | 0.18 | 0.56 | 0.19 |
| | 1,578.9 | −28.7 | | | | −1.9**** | | | 1.03** | 0.001 | 0.58 | 0.22 | 0.65 | 0.22 |
| | 1,497.7 | 133.6 | | | | | 125.6*** | | 0.31* | 0.000 | 0.77 | 0.09 | 0.81 | 0.09 |
| | 1,645.0 | −160.5 | | | | | | 120.1*** | 0.34** | 0.000 | 0.84 | 0.12 | 0.87 | 0.12 |

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; NW, femoral notch width; NWI, femoral notch width index; $\Delta R^2_{adj}$, the change in $R^2$ once $VOL_{QUAD}$ is added; $R^2_{adj}$, adjusted $R^2$ for the entire model; $R^2_{Quad}$, the squared semipartial correlation of the amount of variance in $VOL_{ACL}$ explained only by $VOL_{QUAD}$; $R^2$Tot, total unadjusted $R^2$ for the three-step model; $VOL_{ACL}$, ACL volume; $VOL_{HAM}$, hamstring muscle volume; $VOL_{QUAD}$, quadriceps muscle volume.

*$p < 0.10$.

**$p < 0.05$.

***$p < 0.01$.

****$p < 0.001$.

controls (mean age 26 years) and ACL CSA was greater in those who had trained longer (range 10–25 years) and started training at a younger age (range 9–12 years).[36] On the basis of these findings and our results, it may be feasible to positively impact ACL size and reduce anterior knee laxity through high-intensity resistance training that is designed to optimize lower extremity muscle mass development in young females. We are not aware of any studies to date that have examined ligament adaptions in response to a muscle development training protocol. Appreciating that the quadriceps muscle acts as an ACL antagonist and appropriate quadriceps to hamstring strength ratios are essential for optimal performance and knee joint health, such a program should focus on the entire lower extremity, and not solely on quadriceps development.

Pubertal development is a time when both males and females continue to increase total body mass, but females gain greater relative fat mass while males gain greater relative muscle mass.[26,42–44] By 13–14 years of age, females have accrued most of their muscle, bone, and ligament.,[19,26,45] whereas males continue to accrue muscle through age 18.[26] This is also demonstrated in the regional thigh composition of adolescent volleyball players, where adolescent females had 22% less quadriceps muscle CSA and 44% greater subcutaneous fat at age 16 compared to males, and exhibited no increase in quadriceps muscle CSA from 16 to 18 years, whereas males continued to increase.[42] Should quadriceps muscle volume be a significant contributor to ACL volume, this may explain why smaller relative ACLs,[20,46] and greater anterior knee laxity[47,48] and ACL injury risk[4] emerge in females thereafter. Thus, initiating resistance training to augment muscle mass development during the early to mid-pubertal years (~9–14) may potentially enhance ligament development. This time frame coincides with the timing of the female "adolescent growth spurt" (mean 12.1 ± 1.4 years) when females still have considerable capacity for muscular adaptations.[49] In support of this premise, a systematic review of ACL prevention programs based on age, sex, and program components reported a greater reduction in ACL injury risk when programs targeted middle school and high school athletes; and that greater benefits were derived in those that included lower body strengthening exercises.[50]

In summary, quadriceps muscle volume appears to be a unique contributor to ACL volume once accounting for sex and other body dimensions. This study is limited to a cross-section of a relatively small sample of physically active college-aged individuals. Examining these relationships longitudinally as males and females develop during adolescent growth would shed further light on these associations and the primary drivers of ACL size and integrity. Additionally, larger samples would allow for the entry of multiple body dimensions to determine the unique combination that is most predictive of ACL size and would

**TABLE 5** Semipartial correlations of the independent association of each variable with $VOL_{ACL}$

| | Semipartial correlations Step-2 | | Semipartial correlations Step-3—$VOL_{QUAD}$ entered | | |
|---|---|---|---|---|---|
| | Sex | Body dimension | Sex | Body dimension | $VOL_{QUAD}$ |
| Nondominant limb | | | | | |
| Sex | −0.57 | | 0.01 | | 0.46 |
| Sex + Ht | −0.04 | 0.45 | 0.10 | 0.26 | 0.27 |
| Sex + Mass | −0.13 | 0.40 | 0.02 | 0.13 | 0.26 |
| Sex + BMI | −0.50 | 0.11 | 0.01 | −0.08 | 0.45 |
| Sex + $VOL_{HAM}$ | −0.09 | 0.30 | −0.09 | −0.27 | 0.44 |
| Sex + NW | −0.20 | 0.56 | 0.08 | 0.45 | 0.31 |
| Sex + NWI | −0.66 | 0.63 | −0.15 | 0.54 | 0.31 |
| Dominant limb | | | | | |
| Sex | −0.58 | | 0.05 | | 0.47 |
| Sex + Ht | −0.16 | 0.30 | 0.08 | 0.10 | 0.37 |
| Sex + Mass | −0.11 | 0.43 | 0.07 | 0.19 | 0.27 |
| Sex + BMI | −0.47 | 0.23 | 0.04 | 0.08 | 0.41 |
| Sex + $VOL_{HAM}$ | −0.15 | 0.27 | 0.05 | −0.29 | 0.48 |
| Sex + NW | −0.19 | 0.61 | 0.11 | 0.50 | 0.31 |
| Sex + NWI | −0.66 | 0.58 | −0.05 | 0.52 | 0.40 |
| Limb average | | | | | |
| Sex | 0.58 | | 0.03 | | 0.47 |
| Sex + Ht | −0.11 | 0.38 | 0.08 | 0.18 | 0.33 |
| Sex + Mass | −0.12 | 0.42 | 0.05 | 0.16 | 0.26 |
| Sex + BMI | −0.50 | 0.18 | 0.03 | 0.01 | 0.43 |
| Sex + $VOL_{HAM}$ | −0.12 | 0.29 | −0.02 | −0.29 | 0.47 |
| Sex + NW | −0.17 | 0.61 | 0.10 | 0.50 | 0.31 |
| Sex + NWI | −0.68 | 0.64 | −0.12 | 0.56 | 0.35 |

Abbreviations: ACL, anterior cruciate ligament; BMI, body mass index; Ht, height; NW, femoral notch width; NWI, femoral notch width index; $VOL_{ACL}$, ACL volume; $VOL_{HAM}$, hamstring muscle volume; $VOL_{QUAD}$, quadriceps muscle volume.

provide greater precision of all estimates. Future feasibility and efficacy studies are needed to determine the extent to which a training stimulus can effectively alter the size and structure of the ACL in young maturing females. Understanding the dynamic/modifiable contributions to sex differences in ACL size, and other intrinsic factors that make the ACL more vulnerable to injury may lead to new and impactful approaches to intervention prevention.

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## CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

## AUTHOR CONTRIBUTIONS

Sandra J. Shultz, Randy J. Schmitz, and Anthony S. Kulas substantially contributed to the concept and design, and acquisition of the data. Hsin-Min Wang contributed substantially to the acquisition and reduction of the data. Sandra J. Shultz and Jeffrey D. Labban contributed substantially to the analysis and interpretation of the data. All authors contributed to drafting the paper, revising it critically, and have read and approved the final submitted manuscript.

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