Original Article
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Does Femoral Intercondylar Notch Volume Differ in Anterior Cruciate Ligament-Injured Adult Patients Compared to the Uninjured?: A Meta-Analysis

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Background: Stenotic femoral intercondylar notch is considered as a risk factor for anterior cruciate ligament (ACL) injury and three-dimensional notch volume is used as a marker for the injury. The primary purpose of this study was to assess the difference in notch volume between the ACL-injured and uninjured in men and women combined or stratified by sex. The secondary purpose was to assess the difference in notch volume between the ACL-intact men and women.

Methods: A search of PubMed/Medline, Scopus, Google Scholar, and Cochrane databases from inception to December 9, 2020, was conducted without restrictions using the following terms: ACL, notch, volume, notch volume, femoral notch volume, and intercondylar notch volume. Studies that compared the ACL-injured with uninjured controls were included. Independent extraction of articles by two authors using predefined data fields including study quality indicators was done. All pooled analyses were based on the inverse-variance weighted random effects model and mean difference was chosen as the effect measure.

Results: Nine studies (1,169 knees) qualified for overall analysis (both sexes combined) and significant heterogeneity was observed, which disappeared after pooling studies with age-sex matched controls and those without. Notch volume in the ACL-injured was 0.75 cm^3 (95% confidence interval [CI], 0.53–0.96 cm^3), which was smaller than that in the age- and sex-matched controls. Six studies qualified for analysis in men. Notch volume in the ACL-injured men was smaller, especially when non-contact ACL injury was considered (1.40 cm^3; 95% CI, 1.08–1.73 cm^3). Five studies qualified for analysis in women and ACL-injured women had smaller notch volume irrespective of the mechanism of injury (0.38 cm^3; 95% CI, 0.18–0.59 cm^3). Notch volume of the uninjured men was larger than that of the uninjured women (1.86 cm^3; 95% CI, 1.54–2.18 cm^3).

Conclusions: ACL-injured adults have smaller notch volume than the age- and sex-matched controls. Non-contact ACL-injured males have smaller notch volume compared to ACL-intact males. ACL-injured females have smaller notch volume irrespective of the nature of injury. Men have higher notch volume than women. The quality of evidence is very low to low.

Keywords: *Anterior cruciate ligament, Femur, Risk factors, Notch volume, Stenotic femoral intercondylar notch*

Anterior cruciate ligament (ACL) injuries are one of the most common sports-related injuries and research efforts are directed towards identification of risk factors of ACL injury.[1-3] The rationale behind this search is that once an at-risk knee is identified, preventive strategies can be devised and instituted more effectively. Various risk factors of ACL injury are described and are categorized as intrinsic and extrinsic factors.[4] Risk factors inherent to the individual are called intrinsic factors and include anatomical,

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sex-related, neuromuscular, hormonal, and genetic influences.[4] Sex is considered to be an independent risk factor and women are at a higher risk (> 3–4 times) of non-contact ACL injuries.[5] Among the various anatomical factors, innate knee morphometry—in particular, intercondylar notch geometry—is considered an important predisposing factor for ACL injury.[4,6-8]

Stenotic femoral intercondylar notch is considered as a risk factor and various two-dimensional (2D) notch parameters have been evaluated on radiographs and magnetic resonance imaging (MRI), including notch width (NW), notch width index (NWI), notch angle (NA), notch depth (ND), and notch shape index (NSI).[2,6] Considerable diversity exists in the measurements and no single parameter has been established as a marker of stenotic notch.[9-17] In addition, these 2D notch measurements are not only plane-specific (coronal/axial/sagittal) but also location-specific in a given plane. Recent meta-analyses on these 2D parameters suggest inconsistent association with ACL injury. A meta-analysis by Andrade et al.[18] concluded smaller NW and NWI would be associated with ACL tears. However, they reported very high heterogeneity in their analyses (80% and 93% for NW and NWI, respectively). On closer analysis, the included studies differed in various aspects, most notably on the plane and location of measurements. Li et al.[19] found NW to be smaller in the ACL-injured in both the axial and coronal planes but NWI was smaller in the coronal plane only. High heterogeneity was noted in the meta-analysis regarding NW in the axial plane and almost all meta-analyses pertaining to NWI. Li et al.[20] found NW to be smaller in both men and women, whereas NWI was significantly smaller only in men. Significant heterogeneity was apparent in almost all the meta-analyses including those concerning NW. Presence of such high heterogeneity raises concerns about inconsistency of the results.

As 2D notch parameters can be plane- and location-specific, it is probably unreasonable to expect a single unifying 2D parameter that defines morphology of a complex three-dimensional (3D) space. Intercondylar notch volume (notch volume) being a 3D parameter was proposed to be a better marker for stenotic notch.[21] Smaller notch volume has been associated with ACL injury in some studies.[22] Some authors found smaller notch volume to be an independent risk factor of non-contact ACL injury.[23] On the other hand, some studies have found contradictory results.[24] Significant sex difference has also been suggested among various notch parameters including notch volume,[6,15,23,25] and some authors[26] have suggested separate analysis of male and female data due to this sex difference. While some studies have analyzed notch volume separately in men and women, others have failed to do so.[24] Furthermore, some studies have included only non-contact ACL injury while others have not been restricted on the mechanism of injury.[22]

To the authors' best knowledge, no systematic review or meta-analysis has been conducted yet to assess the association of notch volume with ACL injury. The primary purpose of the current study was to assess the difference in notch volume between the ACL-injured and uninjured when men and women are analyzed together or when each sex is analyzed separately. The secondary purpose was to assess the difference in notch volume between ACL-intact men and ACL-intact women. We hypothesized that smaller intercondylar notch volume would be associated with ACL injury irrespective of sex and that men have larger intercondylar notch volume than women.

METHODS

The study was conducted in compliance with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines,[27,28] and a thorough search of Medline (PubMed), Scopus, Google Scholar, and Cochrane databases was done from inception to December 9, 2020, to retrieve relevant studies that evaluated femoral intercondylar notch volume. Search string used in PubMed was as follows: (((((anterior cruciate ligament) AND (notch)) AND (volume)) OR (femoral notch volume)) OR (femoral intercondylar notch volume)) OR (intercondylar notch volume). No restrictions were placed. Similar search strings were used for all the databases as per the permissible syntax. Two authors (VJ and QA) independently assessed each study in two rounds. First round consisted of screening focused on titles and abstracts while the second round analyzed full texts for eligibility. References given in the included articles were also scrutinized to include additional studies. Any disagreement regarding qualification of study was resolved by discussion at the third round.

Criteria for inclusion were as follows: (1) studies measuring femoral intercondylar notch volume using MRI/computed tomography (CT), (2) comparative study with a control group, (3) exposure of interest being femoral intercondylar notch volume, (4) outcome of interest being ACL injury, and (5) relevant data being available for evaluation. Exclusion of the study was done if it (1) did not include the control group, (2) was a review, letter, or meeting abstract, (3) was animal study, cadaveric study, or studied graft failure after reconstruction, or (4) included pediatric population.

Data Extraction

Data extraction was done systematically by the two aforementioned authors. Following information were recorded from each study: first author's name, year of publication, country of origin, sample size of both groups, sex details, study design, inclusion/exclusion criteria for the comparison groups, and all data relevant to the objectives. Mean difference (MD) was selected as the principal summary measure. Relevant data for calculation of effect size were either directly taken from the study (if available) or were back-calculated using methods described in Cochrane handbook (using *p*-value of *t*-test, *t*-test statistic, confidence interval [CI], sample size, etc.).[29] Subgroups were combined when deemed necessary and if data provided in an article did not allow for calculation of effect measure, the study was discarded from the meta-analysis.

Assessment of Risk of Bias

Both the aforementioned authors independently assessed the methodological quality and susceptibility to bias using Newcastle-Ottawa Scale (NOS).[30] Disagreement was resolved by discussion. Considering the presence of sparse literature, perfect blinding of articles for analysis was not possible; however, journal titles, author names, and origin were blinded from the reviewers at this stage. Reliability of assessment was measured using Cohen's Kappa statistic on IBM SPSS ver. 26.0 (IBM Corp., Armonk, NY, USA).

Statistical Analysis

The data were recorded and managed using Revman 5.3 software, Cochrane collaboration, Oxford, England. Inverse-variance weighted meta-analysis on random effects model was performed and reported. Heterogeneity was evaluated using Q, τ^2 statistic, and I^2 statistic and when present, it was investigated through subgroup analysis using characteristics found important during full text review. A priori consideration was given to this analysis. It was determined at the time of full text review that the studies differed in some clinical aspects and needed exploration. Methods used to calculate notch volume, restriction to non-contact ACL injury, use of injured knee or contralateral healthy knee for measurement, and study methodology were identified as important clinical differences. To assess publication bias, Trim and Fill method and Egger's test were used when appropriate. Sensitivity analysis was done by excluding single study from analysis. Statistical analysis was performed by Revman 5.3. Open source Prometa 3 software was used for those analyses that were not supported by Revman 5.3 (viz Egger's test, sensitivity plots). Statistical significance was considered at $p < 0.05$. Grading of Recommendations Assessment, Development, and Evaluation (GRADE) recommendations were followed to determine quality of evidence.[31] Effect size was reported as MD (95% CI) in cm^3.

RESULTS

The literature search identified 328 articles and a detailed screening process (Fig. 1) yielded 12 studies[14,21-24,32-38] that qualified for the study. Three studies were from the same

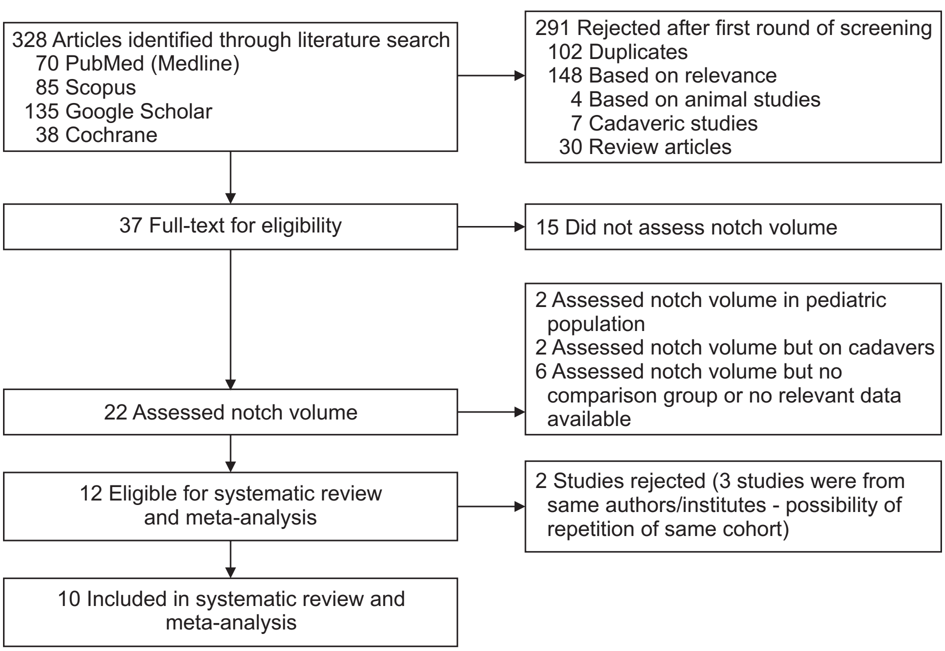

Fig. 1. Flow diagram of detailed screening process during study.

authors/institutions and had overlapping duration of the study.[21,23,38] Possibility of the same cohort of patients being repeated could not be ruled out, hence we decided to include only 1 study[23] out of the 3 studies. We decided to include the study[23] that had the same primary objective as the current study (to compare the intercondylar notch volume between the ACL-injured and uninjured). In addition, it had a larger sample size than the other 2 studies[21,23] and provided sex-related data. In total, 10 studies were finally included in the analysis.[14,22-24,32-37]

All included studies were case-control in design and 6[22-24,33,36,37] of those contained sex-related data. One study was exclusively limited to men.[33] With regards to moderator characteristics that were decided a priori, 5 studies included only non-contact ACL injuries,[14,23,33,34,36] while the others[22,24,32,35,37] were unrestricted/unspecified. The most common method of measurement (6 studies)[22-24,35-37] was on axial MRI sections as per Charlton et al.[25] One study[33] modified the method by including a slice interval, while 3 studies[14,32,34] used different methods. Five studies had matching of controls,[14,22,23,33,36] while the other 5[24,32,34,35,37] had unmatched selection of controls. Contralateral healthy knees were used as a surrogate for measurements of the injured knees in 3 studies[14,35,36] (primarily because of interest in the pre-injury status of ACL volume), while the rest (7 studies)[22-24,32-34,37] used the injured knees.

Table 1. Study Characteristics

Study (year)	Study type/sample size (n)/age (yr)	Comparability of controls/ NOS score	Other study characteristics
Zhang et al. (2019)[23] (assessment)	Retrospective, case control I: 140, C:140 Age: 29.9 ± 6.6	Matched controls (age, sex) Evidence: level III NOS: 7 (3/1/3)	Method by Charlton et al.[25] Used injured knee Only non-contact injuries
Iriuchishima et al. (2021)[32]	Prospective, case control I: 47, C: 41 Median age (I: 26, C: 27)	Controls unmatched Evidence: level III NOS: 5 (2/0/3)	Different method of measurement - 3D CT Used injured knee Nature of injury unspecified
Jha and Pandit (2021)[33]	Retrospective, case control I: 80, C: 80 Age: NA Study limited to males only	Matched controls (age, sex, height) Evidence: level III NOS: 8 (3/2/3)	Modified the method by Charlton et al.[25]: utilized slice interval in addition to slice thickness for calculation Used injured knee Only non-contact injuries
van Eck et al. (2011)[24] (comparison)	Retrospective, case control I: 50, C: 50 Age: 33.3 ± 14.3	Controls unmatched Evidence: level III NOS: 5 (2/0/3)	Method by Charlton et al.[25] Used injured knee Nature of injury unspecified
Wratten et al. (2015)[22]	Retrospective, case control I: 90, C: 90 Age: 31.8 ± 11.3	Matched controls (age, sex) Evidence: level III NOS: 7 (3/1/3)	Method by Charlton et al.[25] Used injured knee Nature of injury unspecified
Oshima et al. (2020)[35]	Prospective, case control I: 19, C: 18 Age: 29.9 ± 10.5	Controls unmatched Evidence: level III (controls were healthy adults) NOS: 5 (3/0/2)	Method by Charlton et al.[25] Used contra-lateral healthy knee Nature of injury unspecified
Whitney et al. (2014)[36]	Prospective, case control I: 88, C: 88 Age: NA	Matched controls (age, sex) Evidence: level III NOS: 9 (4/2/3)	Method by Charlton et al.[25] Used contra-lateral healthy knee Only non-contact injuries
Simon et al. (2010)[14]	Prospective, case control I: 27, C: 27 Age: NA	Matched control (age, sex, weight, height) Evidence: level III NOS: 6 (2/2/2)	Method unspecified Used contra-lateral healthy knee Only non-contact injuries
Taneja et al. (2018)[34]	Prospective, case control I: 50, C: 50 Age: 36.8 ± 9.3	Unmatched control Evidence: level III NOS: 7 (4/0/3)	Different method of measurement Used injured knee Only non-contact injuries
Kim et al. (2013)[37]	Retrospective, case control I: 72, C: 80 Age: 40.91 ± 11.25	Unmatched controls Evidence: level III NOS: 6 (3/0/3)	Method by Charlton et al.[25] Used injured knee Nature of injury unspecified

Values are presented as mean ± standard deviation or number.
NOS: Newcastle-Ottawa Scale, I: sample size of anterior cruciate ligament-injured group, C: sample size of control group, 3D CT: three-dimensional computed tomography, NA: not available.

Risk of bias assessment as per NOS score is shown in Table 1. Two authors (VJ and QA) independently assessed the studies for risk of bias and the inter-rater reliability by Cohen's kappa statistic was 0.883 ($p < 0.0001$). Association with ACL injury was assessed stepwise by first comparing overall (men and women data combined) ACL-injured cases with controls. This was followed by sex-controlled comparison and inter-sex comparison of uninjured controls.

ACL-Injured versus Controls (Overall Data Including Both Sexes)

Nine studies[14,22-24,32,34-37] qualified for this analysis that compared 582 injured knees with 587 controls. Pooled results showed significant difference between cases and controls (MD, –0.40 cm^3; 95% CI, –0.75 to –0.05; p = 0.002) (Table 2). The negative value of MD points towards the ACL-injured group having smaller notch volumes compared to

Table 2. Overall Comparison: Male and Female Combined Analysis (ACL Injured vs. Control)

Comparison*	Total knees (case vs. control)	Mean difference (95% CI, cm^3)	Test for overall effect Z (p-value)	Subgroup difference	Comment
ACL injured vs. controls (male and female combined)[14,22-24,32,34-37]	1,169 (582 vs. 587)	–0.40 (–0.75 to –0.05)	Z = 2.22 (p = 0.03)	NA	Significant heterogeneity requires exploration.
		Q = 29.36, df = 8 (p = 0.0003), I^2 = 73%, τ^2 = 0.18; 95% prediction interval (–1.002 to 0.202)			
Restricted to non-contact injury (4 studies)[14,23,34,36]	612 (305 vs. 307)	–0.57 (–1.02 to –0.11)	Z = 2.43 (p = 0.02)	Q = 0.75, df = 1 (p = 0.38), I^2 = 0%	Restriction to non-contact ACL injury does not affect pooled effect size.
		Q = 10.35, df = 3 (p = 0.02), I^2 = 71%, τ^2 = 0.14			
Unrestricted (5 studies)[22,24,32,35,37]	557 (277 vs. 280)	–0.24 (–0.83 to 0.35)	Z = 0.78 (p = 0.43)		
		Q = 16.97, df = 4 (p = 0.002), I^2 = 76%, τ^2 = 0.31			
Using injured knee (6 studies)[22-24,32,34,37]	902 (449 vs. 453)	–0.38 (–0.83 to 0.06)	Z = 1.68 (p = 0.09)	Q = 0.20, df = 1 (p = 0.66), I^2 = 0%	Use of injured knee or uninjured contralateral knee does not affect pooled effect size.
		Q = 27.35, df = 5 (p < 0.0001), I^2 = 82%, τ^2 = 0.24			
Healthy knee as surrogate (3 studies)[14,35,36]	267 (133 vs. 134)	–0.52 (–0.94 to –0.10)	Z = 2.44 (p =0.01)		
		Q = 1.87, df = 2 (p = 0.39), I^2 = 0%, τ^2 = 0.00			
Standard method to measure (6 studies)[22-24,35-37]	925 (458 vs. 467)	–0.33 (–0.76 to 0.10)	Z = 1.49 (p = 0.14)	Q = 0.41, df = 1 (p = 0.52), I^2 = 0%	Method of measurement of volume does not affect pooled effect size.
		Q = 22.49, df = 5 (p = 0.0004), I^2 = 78%, τ^2 = 0.21			
Other methods (3 studies)[14,32,34]	244 (124 vs. 120)	–0.64 (–1.49 to 0.21)	Z = 1.48 (p = 0.14)		
		Q = 5.60, df = 2 (p = 0.06), I^2 = 64%, τ^2 = 0.36			
Matched controls (4 studies)[14,22,23,36]	690 (345 vs. 345)	–0.75 (–0.96 to –0.53)	Z = 6.74 (p < 0.00001)	Q = 6.46, df = 1 (p = 0.01), I^2 = 84.5%	ACL injured knees had smaller notch volume compared to matched controls.
		Q = 1.77, df = 3 (p = 0.62), I^2 = 0%, τ^2 = 0.00			
Unmatched controls (5 studies)[24,32,34,35,37]	479 (237 vs. 242)	–0.07 (–0.55 to 0.40)	Z = 0.31 (p = 0.76)		
		Q = 10.64, df = 4 (p = 0.03), I^2 = 62%, τ^2 = 0.16			

ACL: anterior cruciate ligament, CI: confidence interval, Q: Cochrane's Q statistic (X^2), df: degrees of freedom, τ^2: tau^2, NA: not available.
*All analyses used inverse-variance weighted random effects model. Unit of effect measure: mean difference in cm^3.
Statistically significant, p < 0.05.

controls. Significant p-value denotes that effect estimate is different from null effect (zero MD). Substantial heterogeneity was noted (p = 0.0003, I^2 = 73%, τ^2 = 0.18) and a subgroup analysis was done based on pre-decided factors. Results of the analysis are detailed in Table 2. Subgroup analysis based on injury mechanism, method of measurement of notch volume, or use of the injured/contralateral knee for measurement did not explain heterogeneity adequately. Heterogeneity was best explained when the studies were grouped according to comparability of controls. Four studies[14,22,23,36] had age and sex matching of controls, while 5[24,32,34,35,37] had unmatched controls. The difference between the two subgroups was statistically significant (p = 0.01) (Table 2). Pooled effect size of studies with matched controls was found to be –0.75 cm^3 (95% CI, –0.96 to –0.53) without any heterogeneity (I^2 = 0%, τ^2 = 0.0). Fig. 2 depicts a forest plot of overall analysis with both sexes evaluated together. Sensitivity analysis by exclusion of a single study (Fig. 3) showed that pooled MD ranged from –0.53 cm^3 (95% CI, –0.83 to –0.22; p = 0.001) to –0.30 cm^3 (95% CI, –0.66 to 0.05; p = 0.097) with heterogeneity I^2 ranging from 59% to 76%. Sensitivity analysis by segregating the prospective and retrospective studies showed no significant differences between the two subgroups (p = 0.729). The prospective group showed similar pooled MD (–0.45; 95% CI, –0.90 to –0.001; p = 0.0491; I^2 = 47.64%; τ^2 = 0.11), while the pooled effect size of the retrospective subgroup was nonsignificant (–0.32; 95% CI, –0.90 to 0.26; p = 0.278). Trim and fill analysis showed insignificant publication bias (Fig. 4) and the estimated effect size was the same as the observed effect size. Egger's linear regression test also revealed no publication bias (intercept 0.72, t = 0.43, p = 0.684).

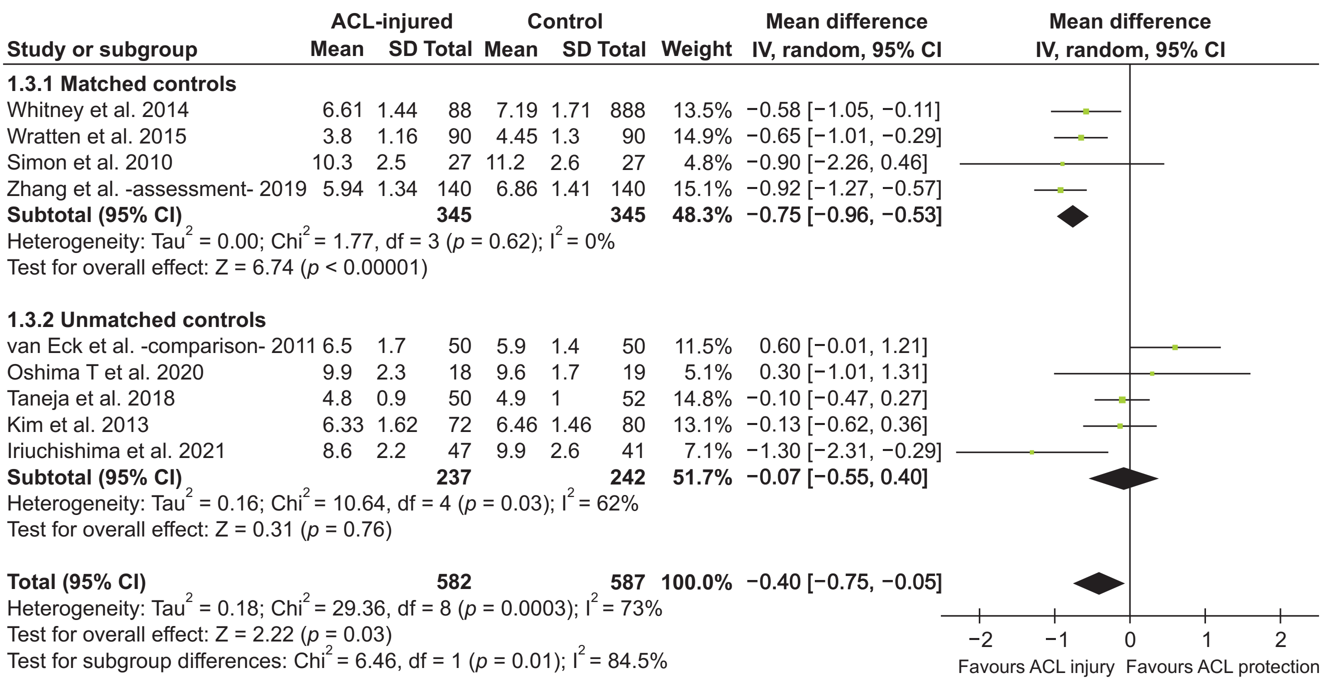

Fig. 2. Forest plot of overall analysis of the anterior cruciate ligament (ACL)-injured vs. control (both sexes considered together). Means in cm^3. SD: standard deviation, IV: inverse variance weighted, Random: random effects analysis, CI: confidence interval, Chi^2: Cochrane's Q, df: degrees of freedom; since effect size is mean difference, null effect is zero.

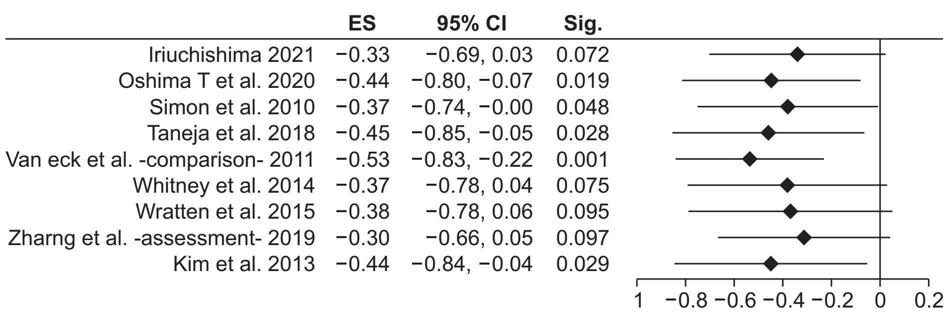

Fig. 3. Sensitivity analysis by exclusion of a single study (overall analysis of the anterior cruciate ligament-injured vs. control; both sexes considered together). ES: effect size (mean difference in cm^3), CI: confidence interval; since effect size is mean difference, null effect is zero.

Male ACL-Injured versus Male Controls

Six studies[22-24,33,36,37)] qualified for this meta-analysis, of which 5 used the same method of measurement. One study utilized the similar method with one modification: used slice interval in addition to slice thickness in the calculation.[33)] Male ACL-injured patients had significantly smaller notch volume compared to controls (pooled MD = –0.71 cm^3; 95% CI, –1.35 to –0.06; $p = 0.03$) but significant heterogeneity was present ($I^2 = 88\%$, $\tau^2 = 0.55$, $p < 0.00001$) (Table 3). Segregation of studies based on mechanism of injury explained the heterogeneity. Studies with restriction to non-contact injury showed negligible heterogeneity ($I^2 = 0\%$, $\tau^2 = 0.02$, $p = 0.28$) and significant difference was present between the two subgroups ($p = 0.006$). Other moderators failed to explain the heterogeneity. Fig. 5 shows a forest plot of this analysis. On sensitivity analysis with exclusion of any single study, pooled MD ranged from –0.50 cm^3 (95% CI, –1.16 to 0.15) to –1.00 cm^3 (95% CI, –1.50 to –0.50). The effect size altered maximally on exclusion of the study with maximal risk of bias.[24)]

Female ACL-Injured versus Female Controls

When only females were considered, 5 studies[22-24,36,37)] qualified and all five used the same method of measurement. Table 4 and Fig. 6 show results of this analysis: females with ACL injury had smaller notch volume than controls (pooled MD, –0.38 cm^3; 95% CI, –0.59 to –0.18; $p = 0.0002$) without any heterogeneity ($I^2 = 45\%$, $\tau^2 = 0.02$, $p = 0.12$).

This difference increased further when only non-contact ACL injuries[23,36)] were considered (pooled MD, –0.54; 95% CI, –0.78 to –0.31; $p < 0.00001$; $I^2 = 0\%$; $\tau^2 = 0.00$); however, this subgroup showed no significant difference with the subgroup that did not restrict[22,24,37)] to non-contact ACL injuries. No subgroup difference was seen based on whether studies used injured[22-24,37)] or healthy contralateral knees[36)] for measurement. Since all studies used the same standard method of measurement, this moderator was rendered irrelevant. Sensitivity analysis showed nonsignificant effect on the pooled effect size. The maximal effect was seen after exclusion of the study with the highest risk of bias,[24)] but the effect size was still significantly different from the null effect (pooled MD, –0.49; 95% CI, –0.66 to –0.32; $p < 0.00001$; $I^2 = 0\%$; $\tau^2 = 0.00$).

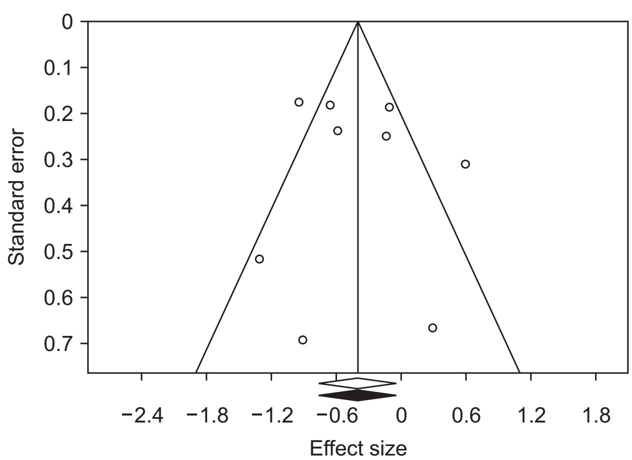

Fig. 4. Trim and fill analysis for publication bias. Visual inspection does not reveal any serious publication bias. Shaded effect size is estimated effect size, which is identical to the observed effect size.

Differences between Male and Female Notch Volume

Using the same 5 studies,[22-24,36,37)] pooled data from male and female control groups were compared and significant difference between the two groups was noted. Notch volume of males was larger by 1.86 cm^3 (95% CI, 1.54 to 2.18) as shown in Fig. 7. While the method of measurement was the same in all, other moderators were rendered irrelevant as this was a comparison of healthy controls.

Due to the inadequate number of studies, formal assessment of publication bias in male and female analysis was not possible owing to limitations of tests.[39)] However, during quality of evidence assessment, some publication bias was suspected and accounted for. Prediction interval of the pooled effect at outcome level was not done due to the inadequate number of studies.[40)]

DISCUSSION

The most important finding of this study is that ACL-injured patients (both men and women combined) have smaller notch volumes than age- and sex-matched controls. When only males are considered, similar relationship exists, which amplifies with non-contact nature of ACL injury. ACL-injured women have significantly smaller notch volume irrespective of the nature of injury. In addition, ACL-intact men have higher notch volume than ACL-intact women. This is in accordance with our hypothesis that ACL-injured patients would have smaller notch volume than ACL-intact controls and that men would have larger notch volumes than women. Summary of findings for important outcomes is tabulated in Table 5 along with GRADE quality of evidence.

Two theories may explain this relationship. First, a smaller notch volume accommodates a smaller, thinner, and vulnerable ACL, which could get injured at lower loads.[21,25,41)] Second, the theory suggests easier impingement of the ACL on the inner wall of the lateral femoral

Table 3. Comparison of ACL-Injured vs. Control: Males Only

Comparison*	Sample (knee)	Mean difference (95% CI)	Significance Z (*p*-value)	Remark	
Males (all studies)[22-24,33,36,37]	578 (292 vs. 286)	–0.71 (–1.35 to –0.06)	z = 2.16 (p = 0.03)	Significant heterogeneity needs exploration.	
		Q = 41.66, df = 5 (p < 0.00001), I^2 = 88%, τ^2 = 0.55			
Males: non-contact (3 studies)[23,33,36]	354 (177 vs. 177)	–1.40 (–1.73 to –1.08)	Z = 8.48 (p < 0.00001)	Subgroup difference Q = 7.48, df = 1 (p = 0.006), I^2 = 86.6%	Non-contact ACL-injured males had smaller notch volumes.
		Q = 2.53, df = 2 (p = 0.28), I^2 = 21%, τ^2 = 0.02			
Males: unrestricted (3 studies)[22,24,37]	224 (115 vs. 109)	–0.08 (–0.97 to 0.81)	Z = 0.18 (p = 0.86)		Subgroup analysis based on mechanism of injury explains heterogeneity.
		Q = 13.04, df = 2 (p = 0.001), I^2 = 85 %, τ^2 = 0.52			
Males: injured knee (5 studies)[22-24,33,37]	524 (265 vs. 259)	–0.64 (–1.37 to 0.09)	Z = 1.71 (p = 0.09)	Subgroup difference Q = 0.55, df = 1 (p = 0.46), I^2 = 0%	Use of injured or healthy contralateral knee for measurement did not differ significantly.
		Q = 41.62, df = 4 (p < 0.0001), I^2 = 90%, τ^2 = 0.62			
Males: healthy knee (1 study)[36]	54 (27 vs. 27)	–1.06 (–1.89 to –0.23)	Z = 2.50 (p = 0.01)		
		NA			
Studies using standard method to measure (5 studies)[22-24,36,37]	418 (212 vs. 206)	–0.50 (–1.16 to 0.15)	Z = 1.51 (p = 0.13)	Subgroup difference Q = 8.46, df = 1 (p = 0.004), I^2 = 88.2%	Method of measurement does not explain heterogeneity adequately.
		Q = 23.73, df = 4 (p < 0.0001), I^2 = 83%, τ^2 = 0.45			
Other methods[33]	160 (80 vs. 80)	–1.62 (–1.99 to –1.25)	Z = 8.64 (p < 0.00001)		
		NA			
Matched controls (4 studies)[22,23,33,36]	444 (222 vs. 222)	–1.21 (–1.61 to –0.81)	Z= 5.95 (p < 0.00001)	Subgroup difference Q = 6.93, df = 1 (p = 0.008), I^2 = 85.6%	Because notch volume is unlikely to vary with age in adults, this association may be spurious.
		Q = 7.52, df = 3 (p = 0.06), I^2 = 60%, τ^2 = 0.10			
Unmatched controls (2 studies)[24,37]	134 (70 vs. 64)	0.32 (–0.75 to 1.38)	Z = 0.59 (p = 0.56)		
		Q = 4.70, df = 1 (p = 0.03), I^2 = 79%, τ^2 = 0.47			

ACL: anterior cruciate ligament, CI: confidence interval, Q: Cochrane's Q statistic (X^2), df: degrees of freedom, τ^2: tau^2, NA: not available.
*All analyses used inverse-variance weighted random effects model. Unit of Effect measure: mean difference in cm^3.
Statistically significant, p < 0.05.

condyle during flexion, especially under tibial plateau rotation shear stress.[21,42)]

The literature regarding notch volume has two major limitations. First, there is a paucity of literature due to tedious and repetitive measurements required on multiple slices for estimation of notch volume. Second, there is considerable diversity in the existing literature. The diversity in literature is exemplified by differential analysis in studies. As with other 2D notch parameters, notch volume has also been found to have significant intersex variations.[22,23,25] In addition, because female sex itself constitutes a separate risk factor[5] for ACL injury, sex can act as a major confounder. For adequate internal validity, this confounder must be dealt with either by study design or appropriate statistical analysis. The literature has been somewhat lacking in this regard. We considered this as a major source of heterogeneity and therefore undertook separate sex analysis. Innate knee morphological risk factors such as notch volume should be evaluated in the setting of a non-contact ACL injury.[43] Contact injuries can occur even in the absence of anatomical risk factors and may act as an effect modifier. Not restricting the cases to "non-contact ACL injuries" by some studies may contribute to statistical heterogeneity and thus was considered as

Study or subgroup	ACL-injured males Mean	SD	Total	Male controls Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
2.3.1 Restricted to non-contact ACL injury								
Whitney et al. 2014	7.78	1.52	27	8.84	1.6	27	14.7%	−1.06 [−1.89, −0.23]
Zhang et al. -assessment- 2019	6.67	1.31	70	7.89	1.55	70	17.6%	−1.22 [−1.70, −0.74]
Jha & Pandit 2021	6.85	1.13	80	8.47	1.24	80	18.3%	−1.62 [−1.99, −1.25]
Subtotal (95% CI)			**177**			**177**	50.6%	**−1.40 [−1.73, −1.08]**
Heterogeneity: Tau^2 = 0.02; Chi^2 = 2.53, df = 2 (p = 0.28); I^2 = 21%								
Test for overall effect: Z = 8.48 (p < 0.00001)								
2.3.2 Unspecified/unrestricted mechanism of injury								
van Eck et al. -comparison- 2011	7.4	1.5	31	6.5	1.5	24	15.0%	0.90 [0.10, 1.70]
Kim et al. 2013	7.25	1.42	39	7.44	1.18	40	16.8%	−0.19 [−0.77, 0.39]
Wratten et al. 2015	4.5	1.1	45	5.3	1.2	45	17.6%	−0.80 [−1.28, −0.32]
Subtotal (95% CI)			**115**			**109**	49.4%	**−0.08 [−0.97, −0.81]**
Heterogeneity: Tau^2 = 0.52; Chi^2 = 13.04, df = 2 (p = 0.001); I^2 = 85%								
Test for overall effect: Z = 0.18 (p = 0.86)								
Total (95% CI)			**292**			**286**	**100.0%**	**−0.71 [−1.35, −0.06]**
Heterogeneity: Tau^2 = 0.55; Chi^2 = 41.66, df = 5 (p <0.00001); I^2 = 88%								
Test for overall effect: Z = 2.16 (p = 0.03)								
Test for subgroup differences: Chi^2 = 7.48, df = 1 (p = 0.006); I^2 = 86.6%								

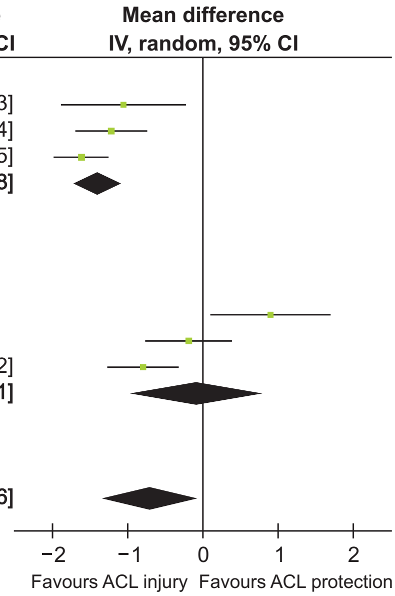

Fig. 5. Forest plot (male anterior cruciate ligament [ACL]-injured vs. male control). Means in cm^3. SD: standard deviation, IV: inverse variance weighted, Random: random effects analysis, CI: confidence interval, Chi^2: Cochrane's Q, df: degrees of freedom; since effect size is mean difference, null effect is zero.

Table 4. Comparison of ACL-Injured vs. Controls: Females Only

Comparison*	Sample (knee)	Mean difference (95% CI)	Significance Z (p-value)	Remark	
Female ACL-injured vs. controls (all studies)[22-24,36,37]	470 (228 vs. 242)	−0.38 (−0.59 to −0.18)	Z = 3.67 (p = 0.0002)	ACL-injured females had smaller notch volumes irrespective of nature of injury or injured/healthy knee used for measurement.	
	Q = 7.26, df = 4 (p = 0.12), I^2 = 45%, τ^2 = 0.02				
Females: non-contact injury (2 studies)[23,36]	262 (131 vs. 131)	−0.54 (−0.78 to −0.31)	Z = 4.51 (p < 0.00001)	Subgroup difference Q = 1.98, df = 1 (p = 0.16), I^2 = 49.5%	Effect size increases in non-contact injury group. No significant difference between subgroups based on mechanism of injury
	Q = 0.98, df = 1 (p = 0.32), I^2 = 0%, τ^2 = 0.00				
Females: unrestricted (3 studies)[22,24,37]	208 (97 vs. 111)	−0.29 (−0.55 to −0.02)	Z = 2.10 (p = 0.04)		
	Q = 3.67, df = 2 (p = 0.16), I^2 = 45%, τ^2 = 0.03				
Females: injured knees (4 studies)[22-24,37]	348 (167 vs. 181)	−0.38 (−0.64 to −0.13)	Z = 2.92 (p = 0.003)	Subgroup difference Q = 0.00, df = 1 (p = 1.00), I^2 = 0%	No significant difference between subgroups based whether injured or healthy contralateral knee was used
	Q = 7.26, df = 3 (p = 0.06), I^2 = 59%, τ^2 = 0.04				
Females: healthy contralateral knee (1 study)[36]	122 (61 vs. 61)	−0.38 (−0.78 to 0.02)	Z = 1.87 (p = 0.06)		
	NA				

ACL: anterior cruciate ligament, CI: confidence interval, Q: Cochrane's Q statistic (X^2), df: degrees of freedom, τ^2: tau^2, NA: not available.
*All analyses used inverse-variance weighted random effects model. Unit of Effect measure: mean difference in cm^3.
Statistically significant, p < 0.05.

another important moderator in the study. Differences in method of measurement contribute to variance in effect size and hence was hypothesized as a moderator. Charlton et al.[25] in 2002 described a method of measurement on axial sections of MRI and this has been subsequently used by most authors. Pooled analysis of reliability of this method is hampered by a paucity of extractable data in the articles; however, interobserver reliability is considered high with

Study or subgroup	ACL-injured females Mean	SD	Total	Female controls Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
van Eck et al. -comparison- 2011	5.2	0.5	19	5.3	0.5	26	23.2%	−0.10 [−0.40, 0.20]
Kim et al. 2013	5.25	1.1	33	5.48	0.98	40	12.8%	−0.23 [−0.71, 0.25]
Whitney et al. 2014	6.09	1.06	61	6.47	1.18	61	16.7%	−0.38 [−0.78, 0.02]
Wratten et al. 2015	3.1	0.7	45	3.6	0.7	45	23.7%	−0.50 [−0.79, −0.21]
Zhang et al. -assessment- 2019	5.21	0.94	70	5.84	0.82	70	23.5%	−0.63 [−0.92, −0.34]
Total (95% CI)			**228**			**242**	**100.0%**	−0.38 [−0.59, −0.18]

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 7.26$, df = 4 ($p = 0.12$); $I^2 = 45\%$
Test for overall effect: Z = 3.67 ($p = 0.0002$)

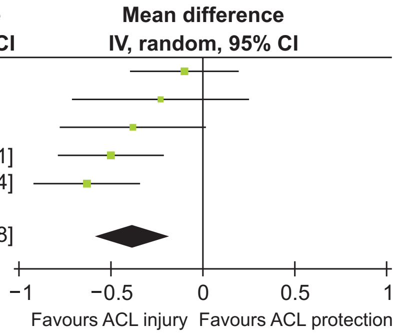

Fig. 6. Forest Plot (female anterior cruciate ligament [ACL]-injured vs. female control). Means in cm³. SD: standard deviation, IV: inverse variance weighted, Random: random effects analysis, CI: confidence interval, Chi^2: Cochrane's Q, df: degrees of freedom; since effect size is mean difference, null effect is zero.

Study or subgroup	Male controls Mean	SD	Total	Female controls Mean	SD	Total	Weight	Mean difference IV, random, 95% CI
Van eck et al. -comparison- 2011	6.5	1.5	24	5.3	0.5	26	15.6%	1.20 [0.57, 1.83]
Wratten et al. 2015	5.3	1.2	45	3.6	0.7	45	24.5%	1.70 [1.29, 2.11]
Kim et al. 2013	7.44	1.18	40	5.48	0.98	40	21.3%	1.96 [1.48, 2.44]
Zhang et al. -assessment- 2019	7.89	1.55	70	5.84	0.82	70	24.2%	2.05 [1.64, 2.46]
Whitney et al. 2014	8.84	1.6	27	6.47	1.18	61	14.4%	2.37 [1.70, 3.04]
Total (95% CI)			**206**			**242**	**100.0%**	**1.86 [1.54, 2.18]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 8.01$, df = 4 ($p = 0.09$); $I^2 = 50\%$
Test for overall effect: Z = 11.49 ($p = 0.0001$)

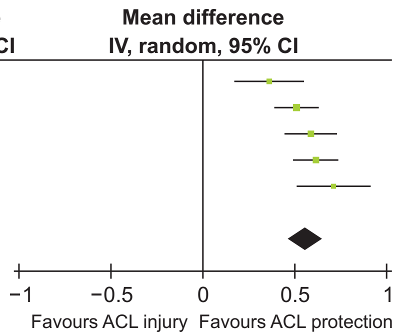

Fig. 7. Forest plot (male controls vs. female control). Means in cm³. SD: standard deviation, IV: inverse variance weighted, Random: random effects analysis, CI: confidence interval, Chi^2: Cochrane's Q, df: degrees of freedom; since effect size is mean difference, null effect is zero.

coefficients ranging from 0.88 to 0.99.[23,25,44] Some studies have used different methods of measurement including modification of the abovementioned method by including slice interval in the formulas, special reformatted volumetric sequences, and CT scans, whereas some did not specify the method of measurement.[14,32-34] There is no data regarding superiority or accuracy of any particular method. Some studies have used the injured knee for notch measurements while others have used healthy contralateral knee as surrogates. It has been shown that the contralateral ACL volume and NWI can be used as surrogates for the injured side[45,46] but the same has not been established for notch volume.

Sex-specific stratified analysis and explanation of heterogeneity by subgroup analysis based on pre-decided moderators contribute to the robustness of the present study. In the overall analysis (with both sexes combined), the significant heterogeneity in results was explained only by matching of controls. Compared to matched controls, ACL-injured patients have a smaller notch volume. This indirectly suggests that men and women have large difference in their notch volumes. Inter-sex comparison of controls also supports this result. Compared to ACL-intact women, ACL-intact men were found to have larger notch volumes. When only men were analyzed, significant heterogeneity was noted (with all the studies included). Further exploration of heterogeneity suggests that smaller notch volume is associated with non-contact ACL-injured men. Partial explanation of heterogeneity was also possible based on study methodology (matching of controls). Those with age-matched controls differed significantly with those with unmatched controls. The matched group, however, retained moderate heterogeneity ($I^2 = 60\%$). Furthermore, since notch volume is unlikely to differ with age, this association could be spurious.[47] The method of measurement and use of injured knee/healthy contralateral knee did not adequately explain the heterogeneity (neither in overall analysis nor in men-only analysis).

Women with ACL injury were found to have significantly smaller notch volume and showed minimal heterogeneity (even when all studies were included). This suggests that notch volume in ACL-injured women is smaller irrespective of the nature of injury. This difference in notch volume amplified further when only non-contact ACL-injured patients were considered. Smaller notches and smaller/thinner ACL may lead to higher rates of in-

Table 5. GRADE Summary of Findings Table for Primary Outcomes

Outcome	Number of knees (study)	Assumed risk[§] (cm^3)	Corresponding risk	Quality of evidence[¶]
ACL-injured vs. control (age, sex matched)	690[†] (4 case control)	4.45–11.20	Notch volume in the ACL-injured is 0.75 cm^3 lesser than in age and sex matched controls (0.53–0.96 cm^3 lesser).[‖]	Low**
Male ACL-injured vs. control*	578[†] (6 case control)	5.30–8.84	Notch volume in ACL-injured males is 0.71 cm^3 smaller than in controls (0.06–1.35 cm^3 smaller).[‖]	Very low[††,‡‡]
Males with non-contact ACL injury vs. control	354[‡] (3 case control)	7.89–8.84	Notch volume in males with non-contact ACL injury is 1.40 cm^3 smaller than in controls (1.08–1.73 cm^3 smaller).[‖]	Very low[‡‡,§§]
Female ACL-injured vs. female control	470[†] (5 case control)	3.60–6.47	Notch volume in ACL-injured females is 0.38 cm^3 smaller than in controls (0.18–0.59 cm^3 smaller).[‖]	Low**,[‡‡]
Male control vs. female control	448[‡] (5 case control)	3.6–6.47 (Female control)	Notch volume in control males is 1.86 cm^3 more than in female controls (1.54–2.18 cm^3 larger).[‖]	Very Low[‖‖,‡‡]

Notch volume measured on magnetic resonance imaging was compared between ACL-injured and uninjured population. Population: adult population, exposure: notch volume, comparator: adult population without ACL injury, outcome: ACL injury, studies: case control.
GRADE: Grading of Recommendations Assessment, Development, and Evaluation, ACL: anterior cruciate ligament, OIS: optimal information size.
*Concern for inconsistency by explaining heterogeneity (by exclusion of study with high risk of bias) was eliminated; however, authors decided to retain all studies and downgrade for inconsistency. [†]OIS criterion met. [‡]OIS criterion not met. OIS calculated using α (0.05), β (0.20), minimal detectable difference in notch volume as 0.380 cm^3. This value was chosen in the absence of an established minimal important difference for notch volume. The value was chosen arbitrarily based on the fact that 0.380 cm^3 was the smallest pooled effect size in the above outcomes. Pooled standard deviations from all the included studies were used and the mean of those standard deviations was considered for calculation of OIS. [§]Calculated by considering means of notch volumes among control groups of included studies. [‖]Minimal important difference for notch volume is unknown. [¶]Quality of evidence starts as low quality as included studies are all observational. **Some concern regarding publication bias cannot be ruled out, but considered nonserious by authors. However, quality of evidence may be rated as "Very low" if one considers serious bias. [††]Concern for inconsistency. [‡‡]Concern for suspicion of some publication bias. [§§]Concern for imprecision. [‖‖]Concern for indirectness.

jury in female athletes compared to male counterparts.[23,48)]

Markers of notch stenosis have been evaluated in other meta-analyses, including the very recent ones.[19,20)] The present study differs from these meta-analyses in two aspects. First, the abovementioned meta-analyses have considered 2D notch parameters such as NW and NWI. The present study considers a 3D parameter instead. Second, the present study anticipated statistical heterogeneity, and a conscious effort to explain the heterogeneity has been made based on very specific moderators that were decided a priori. The successful explanation of heterogeneity in the present study may also be partly because a 3D notch parameter such as notch volume may be a better marker for notch stenosis compared to the multiple, often differently measured 2D parameters.

Notch volume has been correlated with patient characteristics. Three studies[23,24,35)] found moderate to high positive correlations with height and weight (stronger for height), while 1 study[22)] did not find any correlation. The studies differed on many aspects including restriction to non-contact mechanism, use of healthy contralateral knee, and study methodology. Pooled analysis of this correlation was not attempted. Differences in height and weight between the two sexes may contribute to the difference in notch volume. Charlton et al.[25)] adjusted for height and weight and the difference of notch volume observed between the two sexes was rendered insignificant, suggesting that women had smaller notch volumes because of smaller height and weight. Only one study in our analysis matched controls according to height and weight, in addition to age and sex. On a multivariate regression model, neither sex nor height/weight were found to be significantly contributing to variance in notch volume (with ACL and posterior cruciate ligament volumes as factors).[35)] On the contrary, as a predictor for ACL injury, men had a higher odds ratio in a multivariate model.[33)] Meta-regression analysis using height, weight, and sex as covariates would help in this decision, but one would need at least 30 studies for such an analysis.

GRADE summary of findings[49)] for important outcomes are tabulated in Table 5. Being a meta-analysis of observational studies, the quality of evidence starts as low and as a result all the evidence generated here are categorized as very low to low. One of the major reasons for downgrading was inability to meet optimal information size (OIS) criteria and/or suspected publication bias. OIS was calculated using GRADE guidelines.[50)] A minimum notch volume difference to be detected was set arbitrarily at 0.38 cm^3 (based on the lowest pooled effect size in all four meta-analyses) with a standard α (0.05) and β (0.20). A point to be stressed here is that the minimal important difference for notch volume has not been established and therefore this assumption had to be arbitrary.

Clinical implications of these results are many. Firstly, they provide a rationale for further research focusing on the ability to predict ACL injuries (determining appropriate cutoff/critical value of notch volume). Secondly, they underscore the need to screen athletes early to detect those at risk and institute customized training modules (e.g. neuromuscular control and strength training). Thirdly, indications for notchplasty can be explored based on notch volume in order to prevent repeat injury of reconstructed ACL graft and prevention of contralateral injury. Apart from ACL injury, treatment of mucoid degeneration of the ACL also may require objective identification of a stenotic notch. Notchplasty has been recommended in selective cases of mucoid degeneration of the ACL (those with a stenotic notch)[51] and usefulness of notch volume may also be explored in such cases.

Inability to perform formal assessment of publication bias of sex-related outcomes is a major limitation of the study, which stems from scant literature. Broadening of inclusion criteria would neither have helped with the number of studies, nor would it have done justice to the objectives. Possible early reporting bias cannot be ruled out in this setting. Another obvious limitation is that the analysis is based on level III case-control studies, but this is the best available evidence currently. Retaining only prospective studies would leave a single study for sex-based analyses. In the overall analyses, subgroup analysis by segregating prospective and retrospective studies does not explain the heterogeneity, nor does it have adequate OIS, thus creating concerns regarding imprecision as well as inconsistency. Therefore, the authors decided to retain all the studies for evidence generation.

To conclude, ACL-injured adults have smaller notch volume than age- and sex-matched controls. Non-contact ACL-injured men have smaller notch volume compared to ACL-intact men. Women, however, have smaller notch volumes in ACL-injured patients irrespective of the nature of injury. Men have higher notch volume compared to women. The quality of evidence is very low to low.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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