A Majority of Anterior Cruciate Ligament Injuries Can Be Prevented by Injury Prevention Programs

A Systematic Review of Randomized Controlled Trials and Cluster–Randomized Controlled Trials With Meta-analysis

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Background: Anterior cruciate ligament (ACL) injury prevention programs (IPPs) are generally accepted as being valuable for reducing injury risk. However, significant methodological limitations of previous meta-analyses raise questions about the efficacy of these programs and the extent to which meeting current best-practice ACL IPP recommendations influences the protective effect of these programs.

Purpose: To (1) estimate the protective effect of ACL IPPs while controlling for common methodological limitations of previous meta-analyses and (2) systematically categorize IPP components and factors related to IPP delivery to assess the validity of current best-practice IPP recommendations.

Study Design: Systematic review with meta-analysis.

Methods: A systematic search of 5 electronic scientific databases was conducted to identify studies testing the efficacy of ACL IPPs. Studies were included if (1) the intervention aimed to prevent ACL injury, (2) the incidence rate (IR) or other outcome data that made it possible to calculate the IR for both the intervention and control groups were reported, and (3) the study design was a prospective randomized controlled trial (RCT) or cluster-RCT.

Results: Of the 2219 studies screened, 8 studies were included in the quantitative synthesis, and their analysis revealed a significant reduction in ACL IR when athletes received IPPs (IR ratio = 0.47; 95% CI, 0.30-0.73; $P < .001$). The majority of included IPPs tended to meet minimum best-practice recommendations and incorporated plyometric, strengthening, and agility exercises along with feedback on proper landing technique. However, the specific exercises included in each IPP and key factors related to IPP delivery were highly variable.

Conclusion: Despite limiting the analysis to only high-quality studies and controlling for time at risk and potential clustering effects, the study showed that ACL IPPs had a significant protective effect and reduced injury rates by 53%. However, significant variability in the specific exercises and the manner of program delivery suggests that ACL IPPs may be able to be designed within an overarching best-practice framework. This may allow practitioners the flexibility to develop IPPs that meet the specific characteristics of the target population and potentially increase the likelihood that these programs will be widely adopted and implemented.

Keywords: anterior cruciate ligament; injury prevention; NATA position statement; implementation; intervention efficacy; lower extremity injuries

Anterior cruciate ligament (ACL) injury is devastating to an athlete's career, as this injury is associated with significant emotional trauma[33] and a substantial likelihood that the athlete will not return to a competitive level of sport.[1,2] Patients with ACL injury exhibit lower self-reported knee function[8,13] and quality of life[9] and greater risk of being overweight[48] and developing early-onset knee joint osteoarthritis.[11,25,29] Accordingly, a number of different ACL injury prevention programs (IPPs) have been developed and evaluated in interventional studies over the past 2 decades.[‖]

In an effort to summarize the efficacy of these ACL IPPs, no fewer than 11 meta-analyses and a meta-analysis of meta-analyses on this topic have been conducted since 2006.[¶] Although most previous meta-analyses generally

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‖References 3, 14, 17, 19, 23, 27, 36, 40, 41, 45.

¶References 6, 12, 15, 16, 18, 28, 37, 38, 43, 44, 46, 49.

support the conclusion that IPPs are efficacious for reducing ACL injury risk,[6,12,28,37,44,49] the magnitude of the reported summary effects varies widely—from no significant effect up to a 60% reduction in injury rate.[6,12,15,28,44,49] Although some of the variability is likely driven by the relative efficacy of the different IPPs included in each meta-analysis, all previous ACL IPP meta-analyses exhibit at least 1 of the following 3 methodological limitations that have the potential to dramatically influence the magnitude of the summary effect that was reported: (1) not excluding non–randomized controlled designs, (2) not accounting for participant time at risk, or (3) not adjusting for potential clustering effects (Figure 1).

First, all but 1 of the previous meta-analyses on ACL IPPs included studies that used lower quality, nonrandomized designs.[#] However, because "pooling data (meta-analysis) from papers with a high risk of bias actually compounds the bias" rather than eliminating it,[47] the inclusion of data from nonrandomized studies likely incorporates biases into these previous meta-analyses that could substantially skew the results.[4] Second, half of the previous meta-analyses on ACL IPPs used odds ratios (ORs) as the effect estimate for IPP efficacy.[15,18,28,37,38,49] Unfortunately, ORs do not account for potential differences in time at risk (ie, athlete exposure [AE]) between intervention and control participants, and as a result it is recommended that injury rates that do account for time at risk be used to allow for a more direct comparison between groups.[21] Third, although the highest quality ACL IPP interventional studies often used a cluster–randomized controlled trial (RCT) design,[10,12,32,39-41,45] this type of design can potentially introduce a confounder due to a clustering effect.[20] However, only 1 previous meta-analysis accounted for potential clustering effects when synthesizing data from multiple cluster-RCTs.[6] Unfortunately, these methodological limitations of previous ACL IPP meta-analyses result in uncertainty about how efficacious ACL IPPs truly are for reducing injury risk.

Another challenge in evaluating ACL IPP interventions is that many of the efficacy studies use different exercises in their programs and apply these programs to athletes from diverse populations using a variety of delivery methods. Accordingly, rather than identify a single, optimal ACL IPP, a recent position statement on the prevention of ACL injury by the National Athletic Trainers' Association (NATA) recommended that ACL IPPs include at least 3 of the following exercise types: strength, plyometrics, agility, balance, and flexibility, along with feedback on proper exercise technique.[34] However, given that these recommendations were developed by experts following the synthesis of existing literature that included lesser quality studies with a high risk of bias, it is also unknown whether ACL IPPs that meet these minimum recommendations have a more favorable effect than programs that do not.

The primary purpose of this systematic review and meta-analysis was to answer the following clinical question: What is the estimated protective effect of ACL IPPs when controlling for study quality (only RCT or cluster-RCT designs), participant time at risk, and potential clustering effects? We also sought to assess whether meeting current clinical recommendations has an influence on any protective effect elicited by the IPP and to systematically describe factors related to ACL IPP delivery.

METHODS

Data Sources

A 2-step search strategy was used to identify the relevant literature. First, a systematic search of 5 electronic scientific databases, PubMed, MEDLINE, CINAHL, SPORTDiscus, and the Cochrane Central Register of Controlled Trials databases, was performed on March 19, 2018. Key search terms including ACL injury, prevention intervention, and RCT and their synonyms were used to search for related study articles. The key search terms and their synonyms within each filter (ACL injury/prevention intervention/RCT) were combined using the Boolean operator "OR," and all 3 filters were combined to form 1 search using the Boolean operator "AND." No limitations were imposed on the date of publication. Table 1 includes specific key terms and their synonyms. Second, the reference lists of previous meta-analyses on this topic were manually searched for additional papers not already identified.

Eligibility Criteria

To address the methodological concerns found in previous meta-analyses, studies were included only if they met the following criteria: (1) the intervention aimed to prevent ACL injury, (2) the incidence rate (IR) or other outcome data such as injury counts and athlete exposures (ie, time at risk) that made it possible to calculate ACL IR for both the intervention and control groups were reported, and (3) the study used a prospective RCT or cluster-RCT design. Review articles, editorials, lectures, commentaries, abstracts, case studies, surgical techniques, or articles that were not peer reviewed or not written in English were excluded.

[#]References 6, 12, 16, 18, 28, 37, 38, 43, 44, 49.

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Meta-analysis \ Methodological Limitations	Excluded Non-RCTs?	Accounted for Time at Risk?	Adjusted for Clustering?
Grindstaff et al. (2006)	No	Yes	No
Hewett et al. (2006)	No	No	No
Yoo et al. (2010)	No	No	No
Sadoghi et al. (2012)	No	No	No
Sugimoto et al. (2012)	No	Yes	No
Gagnier et al. (2013)	No	Yes	No
Myer et al. (2013)	No	No	No
Donnell-Fink et al. (2015)	No	Yes	Yes
Grimm et al. (2015)	Yes	No	No
Taylor et al. (2015)	No	Yes	No
Petushek (2010)	No	No	No

Figure 1. Previous meta-analysis heat map. RCT, randomized controlled trial.

TABLE 1
Search Terms[a]

Group	Search Terms
ACL injury (outcome)	**OR** “knee” [All Fields] **AND** “injur*(tiab)” [All Fields]
	OR “knee injur*(tiab)” [All Fields]
	OR “knee” [All Fields] **AND** “trauma*(tiab)” [All Fields]
	OR “knee trauma*(tiab)” [All Fields]
	OR “anterior cruciate ligament” [All Fields] **AND** “injur*(tiab)” [All Fields]
	OR “anterior cruciate ligament injur*(tiab)” [All Fields]
	OR “ACL” [All Fields] **AND** “injur*(tiab)” [All Fields]
	OR “ACL injur*(tiab)” [All Fields]
	OR “anterior cruciate ligament” [All Fields] **AND** “tear*(tiab)” [All Fields]
	OR “anterior cruciate ligament tear*(tiab)” [All Fields]
	OR “ACL” [All Fields] **AND** “tear*(tiab)” [All Fields]
	OR “ACL tear*(tiab)” [All Fields]
	OR “anterior cruciate ligament” [All Fields] **AND** “ruptur*(tiab)” [All Fields]
	OR “anterior cruciate ligament ruptur*(tiab)” [All Fields]
	OR “ACL” [All Fields] **AND** “ruptur*(tiab)” [All Fields]
	OR “ACL ruptur*(tiab)” [All Fields]
	OR “lower limb” [All Fields] **AND** “injur*(tiab)” [All Fields]
	OR “lower limb injur*(tiab)” [All Fields]
	OR “lower extremity” [All Fields] **AND** “injur*(tiab)” [All Fields]
	OR “lower extremity injur*(tiab)” [All Fields]
AND	“prevention*(tiab)” [All Fields] **AND** “control*(tiab)” [All Fields]
Intervention	**OR** “prevent*(tiab) and control*(tiab)” [All Fields]
	OR “prevent*(tiab)” [All Fields]
	OR “injur*(tiab)” [All Fields] **AND** “prevent*(tiab)” [All Fields]
	OR “injur*(tiab) and prevent*(tiab)” [All Fields]
	OR “injur*(tiab)” [All Fields] **AND** “avoidance *(tiab)” [All Fields]
	OR “injur*(tiab) and avoidance *(tiab)” [All Fields]
AND	“randomiz*(tiab) controlled trial*(tiab)” [All Fields]
Study design	**OR** “cluster randomiz*(tiab) controlled trial*(tiab)” [All Fields]
	OR “RCT*(tiab)” [All Fields]
	OR “cluster RCT*(tiab)” [All Fields]

[a]ACL, anterior cruciate ligament; RCT, randomized controlled trial.

Study Selection

Study selection was conducted in 3 steps: title review, abstract review, and full-text review. The first and third authors independently screened articles identified during the database search for eligibility based on review of the title and then the abstract. For the title and abstract reviews, articles for which the 2 authors disagreed were included in the next step. For full-text review, any disagreements were resolved by consensus of the fourth and senior authors (J.O., M.F.N.). Interrater agreement was calculated by use of the Cohen kappa coefficient (κ). Magnitude guidelines have been suggested by Landis and Koch,[24] who characterized values less than 0 as indicating no agreement, 0-0.20 as slight agreement, 0.21-0.40 as fair agreement, 0.41-0.60 as moderate agreement, 0.61-0.80 as substantial agreement, and 0.81-1 as almost perfect agreement.

Quality Assessment

The Physiotherapy Evidence Database (PEDro) scale was used to assess the quality of included studies. The scale exhibits moderate reliability and helps to determine internal validity (intraclass correlation, 0.56; 95% CI, 0.57-0.76[26]). Two reviewers (Y.-L.H., C.M.S.M.) independently assessed each study's quality. In instances where study quality ratings differed, the 2 reviewers discussed disagreements until consensus was reached.

Data Extraction and Analysis Procedures

The extracted information provided details regarding ACL injury counts, incidence rate ratio (IRR) of ACL injuries, AEs for intervention and control groups, participants (the total number of the sample, age, and sex), publication year, sports, frequency and duration of prevention programs, and prevention programs. If the IRR was not reported, it was calculated by dividing the number of ACL injuries by the total AEs for intervention and control groups, respectively. Characteristics and findings of all included studies were synthesized.

Prespecified Subgroups

The NATA position statement recommends that ACL IPPs should include, at minimum, technical feedback and exercises from at least 3 of the following exercise categories: strength, plyometrics, agility, balance, and flexibility.[34] Therefore, to evaluate whether the ACL IPPs used in each study met the minimum recommendations, the IPPs were independently reviewed by 2 authors (Y.-L.H. and C.M.S.M.) to categorize exercises included in each program according to their clinical expertise and the definitions put forward in the best-practice recommendations.[34] The reviewers were blinded to both study authors and journals published.

Statistical Analysis

The IRRs from individual studies were pooled into a meta-analysis through use of Comprehensive Meta-Analysis Software (version 3, 2014), and a summarized IRR was calculated. Moderator analysis, according to the prespecified subgroups, was planned for meeting or not meeting minimum ACL IPP best-practice recommendations. Statistical heterogeneity was assessed through the Cochran Q test and the I^2 index test. I^2 reflects the proportion of the observed variability in effect among studies that is due to true differences in effect. Two methods were used to explain heterogeneity in effects among studies. As a guide to interpreting the I^2 index, 0% to 20% represents low heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% considerable heterogeneity.[4]

A cluster-RCT study design was used in the majority of included studies.[14,32,39-41,45] As a result, the potential for a clustering effect needed to be considered because clustered samples tend to be more similar to each other with respect to important confounders than those assigned truly at random.[20] In addition, these studies applied the intervention at the cluster level (eg, team) whereas the outcomes were measured at the individual level (eg, player). The design effect (DE) was used to estimate the extent to which the sample size should be inflated to accommodate for the homogeneity in the clustered data:

$$\mathrm{DE} = 1 + (\mathrm{n} - 1) * \mathrm{p},$$

where n = average cluster size and p = intracluster correlation coefficient (ICC).

Through use of the ICC, the DE was obtained to address clustering effect in this study. As suggested by a Cochrane handbook for systematic reviews of interventions, the numbers of ACL injuries for each study were divided by DE.[4] The adjusted numbers of ACL injuries were used to calculate the adjusted IRR.

Risk of Bias Assessment

A funnel plot, Orwin fail-safe N, and Egger[42] regression test were used to evaluate the risk of publication bias. A funnel plot is used as a visual aid for detecting publication bias. The Orwin fail-safe N computes the number of studies with a null effect size needed to reduce the overall effect to clinical nonsignificance.[22] The Egger regression test was used to quantify the bias by using the actual values of the effect sizes and precision.[42]

RESULTS

Search Results

The initial database search using PubMed, MEDLINE, CINAHL, SPORTDiscus, and the Cochrane Central Register of Controlled Trials databases yielded 4033 results. A flowchart of the selection process is displayed in Figure 2. After duplicates were removed, 2219 studies remained. Of these, 2170 studies were removed after review of the title and abstract. After 4 additional studies were identified through previous meta-analyses, a total of 53 studies were assessed for study eligibility. Following this assessment, 45 studies were removed because they did not contain ACL-specific injury data (n = 34), were written in Chinese (n = 1), were not peer reviewed (n = 1), were review papers (n = 3), or were abstracts (n = 6).

After the full-text review, the primary reviewers (Y.-L.H. and C.M.S.M.) agreed on the exclusion of 45 studies and the inclusion of 4 studies. However, the reviewers disagreed on 4 articles because the ACL IR, injury counts, and/or participant time at risk for both the intervention and the control groups were not explicitly reported, which led to differing interpretations about whether ACL IRs could be calculated for each group. These articles were reviewed independently for eligibility by 2 additional authors (J.O., M.F.N.), who agreed to include all 4 studies

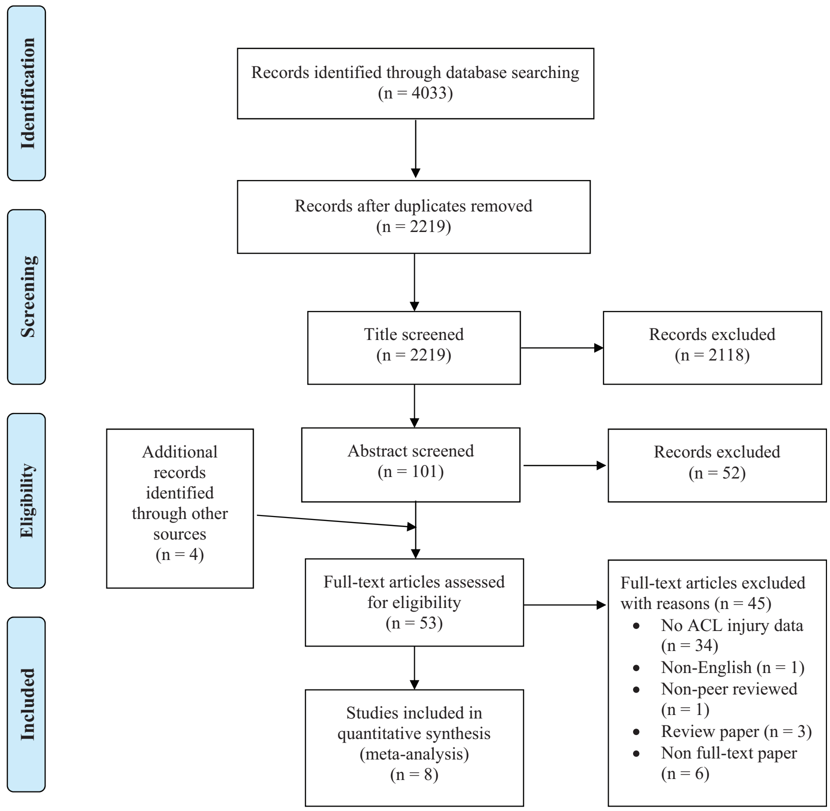

Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for study selection.

TABLE 2
Summary of the Included Studies[a]

Lead Author (Year)	Study Design	PEDro Scores	Sample Size	Sex	Age of Participants, y	Sports
Foss[10] (2018)	Cluster RCT	5	474	Female	Mean ± SD, 14.0 ± 1.7	Soccer, basketball, and volleyball
Gilchrist[14] (2008)	Cluster RCT	6	1435	Female	Mean, 19.88	Soccer
LaBella[23] (2011)	RCT	9	1495	Female	Mean ± SD, 16.19 ± 1.53 (intervention); 16.22 ± 1.06 (control)	Soccer
Olsen[32] (2005)	Cluster RCT	9	1837	Male and female	Range, 15-17	Handball
Silvers-Granelli[39] (2017)	Cluster RCT	7	1525	Male	Range, 20-22	Soccer
Söderman[40] (2000)	Cluster RCT	5	140	Female	Mean ± SD, 20.4 ± 4.6 (intervention); 20.5 ± 5.4 (control)	Soccer
Steffen[41] (2008)	Cluster RCT	8	2092	Female	Range, 13-17	Soccer
Waldén[45] (2012)	Cluster RCT	9	4564	Female	Range, 12-17	Soccer

[a]PEDro, Physiotherapy Evidence Database scale; RCT, randomized controlled trial.

in the analysis because they determined that the information reported in the studies was sufficient to allow for calculation of ACL IR. As a result, 8 studies were included in our final analysis. The agreement between reviewers during the study selection process was assessed using the Cohen kappa, and acceptable agreement was achieved ($\kappa = 0.70$; 95% CI, 0.43-0.98).

Study Characteristics

The characteristics of all studies included in this analysis are presented in Table 2. The publication date ranged from 2000[40] to 2018.[10] The number of participants in the individual studies ranged from 140[40] to 4564.[45] Across all studies, a total of 13,562 participants were included.

Study name	Group by Meet or Not meet NATA recommendation	Rate ratio	Lower limit	Upper limit	Z-Value	p-Value
Gilchrist et al., 2008	Meet	0.584	0.244	1.399	-1.206	0.228
LaBella et al., 2011	Meet	0.273	0.055	1.351	-1.591	0.112
Olsen et al., 2005	Meet	0.280	0.077	1.017	-1.935	0.053
Silvers-Granelli et al., 2017	Meet	0.235	0.069	0.808	-2.300	0.021
Steffen et al., 2008	Meet	0.792	0.213	2.948	-0.348	0.728
Walden et al., 2012	Meet	0.433	0.175	1.072	-1.810	0.070
Soderman et al., 2000	Not Meet	5.492	0.614	49.139	1.523	0.128
Foss et al., 2018	Uncertain	0.434	0.039	4.785	-0.682	0.495
	Overall	0.470	0.303	0.731	-3.349	0.001

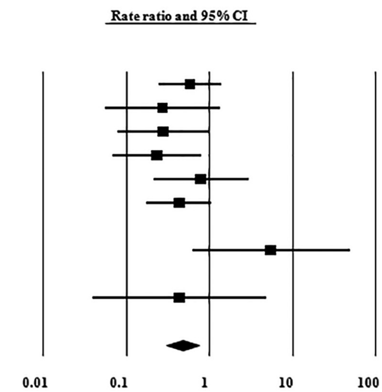

Figure 3. Forrest plot for every study included in this analysis. The prevention program used in the study by Foss et al[10] was classified as ''uncertain'' because it is unclear whether feedback was delivered in the intervention. NATA, National Athletic Trainers' Association.

Publication Bias

Asymmetry was not visible when a funnel plot was used. Orwin fail-safe N revealed that an additional 270 studies with null effects would be needed to reduce the overall effect size to a clinically nonsignificant outcome (standard difference in means, 0.10). More specifically, the summary effect of this meta-analysis would be a clinically nonsignificant outcome if 270 studies with null effects (effect size from 0 to 0.1) were to be added to the analysis. In addition, the estimated bias coefficient from the Egger test is 0.84 with an SE of 1.27 (P = .53). The test result indicated that there is no evidence for asymmetry and therefore no publication bias.

Quality Assessment

Results of quality assessment using the PEDro scale showed a range of 5 to 9 with an average score of 7.25 out of 10 (Table 2). A common reason for a reduction in the PEDro scale score was that no study blinded all participants.

Heterogeneity

The Cochrane Q-test value was not statistically significant (Q value, 7.98; df, 7; P = .33). The I^2 value was 12.4%, which indicates low heterogeneity. Based on this result, it was concluded that heterogeneity was not present, and the overall intervention effect was assessed by use of a fixed-effect model.

Overall Intervention Effects

The study results revealed a statistically significant reduction in ACL injury incidence rate when athletes received ACL IPPs (Figure 3) (IRR, 0.47; Z, –3.35; 95% CI, 0.30-0.73; $P < .001$). The rate of ACL injury was 53% less in athletes who received IPPs compared with the athletes who did not receive IPPs.

Sensitivity Analysis

Although this study was originally designed to account for potential clustering effects by applying the average ICC calculated from the values reported in the individual studies, this approach was not possible because none of the included studies reported ICC. To address the potential clustering effects, a sensitivity analysis was conducted to test the effect that different clustering effects would have on IRR using the approach described by Donnell-Fink et al.[6] We evaluated 2 ICCs, 0.00 (raw data) and 0.08, the latter of which was chosen because the maximum reported ICC by Donnell-Fink et al was 0.071. Assuming no existence of a clustering effect, the raw summary effect of the IPPs was 0.470. The summary effect became 0.484 when the ICC was assumed to be 0.08.

IPP Characteristics and Subgroup Analysis

Table 3 summarizes the characteristics of the IPPs included in the overall analysis. All but 2 IPPs[10,42] met the minimum best-practice recommendations of having at least 3 exercise components in addition to providing feedback on proper exercise technique (Table 3). The specific exercises included in each study as well as the methods of delivery and training were highly variable. Finally, although IPP quality relative to best-practice recommendations was identified a priori as a potential moderator of the efficacy of the ACL IPPs to be explored in this study, this subgroup analysis was not conducted given the absence of significant heterogeneity in effects across studies.

DISCUSSION

By (1) including only high-quality RCT or cluster-RCT studies with an average PEDro score of 7.5 compared with an average of 4.7 in previous meta-analyses,[28,43,44] (2) controlling for time at risk, and (3) accounting for clustering effects, this meta-analysis comprehensively addresses 3 major methodological limitations found in previous meta-

TABLE 3
Multicomponent Breakdown of Anterior Cruciate Ligament Injury Prevention Programs[a]

Lead Author (Year)	Strength	Plyometrics	Agility	Balance	Flexibility	Feedback Provided
Waldén[45] (2012)[b]	Yes—SL/DL squat, pelvic bridge, prone plank, forward lunge	Yes—SL hop forward/backward, side-to-side hop (SL landing), quick step to hop (SL landing), DL jump with ball header	Yes—SL hop to side hop, DL jump with ball header	Yes—SL squat, lunge	No	Yes—coaching staff
Steffen[41] (2008)[b]	Yes—prone/side plank, Nordic hamstring	Yes—SL hop forward/backward, side-to-side hop, zigzag shuffle, bounding	Yes—zigzag shuffle	Yes—cross-country skiing, SL stance chest pass, SL stance forward bend, SL stance figure-of-8	No	Yes—coaching staff and teammates
Olsen[32] (2005)[b]	Yes—Nordic hamstring, DL squat, DL squat on unstable surface	Yes—bounding, forward jumps, jump shot landing	Yes—carioca, parade, forward running with intermittent stops, speed runs, planting and cutting	Yes—DL ball pass unstable surface, SL squat unstable surface, DL squat unstable surface, ball bounce with eyes closed unstable surface, perturbations on unstable surface	Yes—forward running with heel kicks, forward running with knee lifts, forward running with trunk rotation	Yes—teammates
Gilchrist[14] (2008)[b]	Yes—forward lunge, Nordic hamstring, SL heel raises	Yes—DL jump with ball header, SL barrier hop, scissor jumps	Yes—DL jump with ball header, shuttle run, diagonal run, bounding running	No	Yes—calf stretch, quad stretch, figure-of-4 hamstring stretch, groin/adductor stretch, hip flexor stretch	Yes—coaching and sports medicine staffs
Söderman[40] (2000)	No	No	No	Yes—SL stance unstable surface, SL stance “drawing figures” unstable surface, SL stance with wall ball pass	No	No
LaBella[23] (2011)[b]	Yes—DL squat, prone/side plank, forward/lateral walking lunge, heel raises, prone lift	Yes—broad jumps, scissor jumps, ankle bounces, tuck jumps, 180 jumps, squat jumps, DL barrier hop, SL hop hop hold, jump jump vertical jump, SL hop for distance	Yes—shuttle run, diagonal run, lateral shuffle	Yes—SL hop hop hold, SL hop for distance	Yes—high knee skipping, high knee carioca, arm swings, trunk rotations, leg swings, side shuffles with arm swings	Yes—coaching staff
Silvers-Granelli[39] (2017)[b]	Yes—prone/side plank, squat to toe raise	Yes—vertical jumps	Yes—planting and cutting, quick forward and backward, circling partner, shoulder contact	Yes—SL stance with ball hold	Yes—hip in/hip out	Yes—coaching staff
Foss[10] (2018)	Yes—SL RDL, Swiss ball back hyperextensions, box double crunch, Bosu lateral crunch, Bosu DL pelvic bridges, Bosu swimmers, Bosu double-knee hold	Yes—lunge jumps, hop to stabilization and reach	Yes—unanticipated hop to stabilization	Yes—lateral jump and hold, Bosu double-knee hold, SL lateral Airex hop-hold, unanticipated hop to stabilization, hop to stabilization and reach, Airex hop-hold	No	Unclear[c]

[a]Please refer to specific journal articles for full names, descriptions, progressions, and explanation of exercises. DL, double-legged; RDL, Romanian dead lift; SL, single-legged.
[b]Study meets minimum best-practice recommendations for anterior cruciate ligament injury prevention programs.[38]
[c]Initial correspondence with author regarding feedback was not clear, and subsequent requests for clarification were not answered.

analyses, thus providing the strongest evidence to date to support that ACL IPPs have a significant protective effect and can reduce the rate of ACL injury by 53% (Figure 3). This is also the first investigation to systematically evaluate implementation-related factors for each IPP and to categorize each program using the framework put forward in a recent position statement on ACL injury prevention.[34] We found that although the vast majority of the IPPs included in our analysis met the minimum best-practice recommendations, the actual content of IPPs within this general framework and the method of program delivery were highly variable (Table 3).

ACL IPP Efficacy

The magnitude of the effect of IPPs on ACL injury reported in previous meta-analyses varies from no significant effect up to a 62% risk reduction,[6,12,15,28,44,49] with the uncertainty about how efficacious ACL IPPs truly are potentially driven by the methodological limitations. The current study provides greater confidence in the estimated 53% reduction in ACL injury rate because our analysis addressed 3 major methodological limitations common to previous meta-analyses on this topic (see Figure 1).

First, 10 of the 11 previous meta-analyses combined data from nonrandomized studies. Not only is this concerning from a theoretical perspective, as the inclusion of nonrandomized studies in a meta-analysis perpetuates errors and compounds the bias potentially introduced by lower quality study designs,[47] but the results from 3 recent meta-analyses indicated a real possibility that the previously reported IPP effect estimates may have been inflated. Gagnier et al[12] reported that IPPs reduce the rate of ACL injuries by approximately 51% but that there was a stronger estimated effect in the included nonrandomized studies. Similarly, Donnell-Fink et al[6] found that higher quality studies such as RCTs tended to be associated with more conservative efficacy effect estimates. In fact, the only prior ACL IPP meta-analysis limited to RCTs[15] reported a more conservative—and nonsignificant—effect estimate (44%) than the majority of meta-analyses that included lower quality study designs.[6,16,18,28,38,43,49] Although the lack of statistical significance in that study is likely due to insufficient power secondary to a focus on a single sport (soccer) and inclusion of just 4 studies,[15] the results contributed to concerns that previous ACL IPP efficacy estimates may have been unduly influenced by the inclusion of non-RCT study designs.

Second, the potential arises that the efficacy estimates of previous meta-analyses may have been influenced by the fact that more than half of these studies used ORs that do not account for potential differences in the actual time at risk between intervention and control groups (see Figure 1). As a result, the calculated summary effects in these studies could be inflated (or minimized) simply as a result of differences in the time at risk between groups, rather than the true efficacy of the intervention.[21]

Third, only 1 previous meta-analysis attempted to control for potential clustering effects, which can result in an overestimation of the true effect of an intervention[6] (see Figure 1). Although we were unable to directly address potential clustering effects using the methods described by Donnell-Fink et al,[6] given that none of the studies included in our analysis reported ICC, we used a sensitivity analysis to determine the influence that clustered designs might have had on our calculated summary effect. As a result, the current results that we obtained using only Level 1 studies while also accounting for participant time at risk and potential clustering effects provide strong evidence to support that the use of IPPs in team sports can reduce ACL injury rates by up to 53%.

ACL IPP Components and Implementation-related Factors

This investigation is also the first to (1) categorize the included IPPs against the prevention framework put forward in the recent NATA best-practice recommendations[34] and (2) systematically describe IPP components and other program characteristics that can affect IPP implementation (Table 3).

The challenge of the heterogeneous nature of ACL IPPs has been identified in previous meta-analysis reviews[6,49] and has resulted in conflicting reports with respect to the optimal combination of exercises to be included in an IPP.[6,37,49] Accordingly, rather than identify any specific combination of exercises, a recent best-practice statement on ACL injury prevention simply recommends that an IPP should include at least 3 of the following exercise types: strength, plyometrics, agility, balance, and flexibility.[34] However, as this recommendation was developed by synthesizing existing literature that included studies of relatively low quality and a high risk of bias, a secondary aim was to determine whether IPPs meeting the minimal criteria have a more favorable effect than IPPs that do not. Although we were not able to conduct this subgroup analysis given the lack of significant heterogeneity in effect sizes and the fact that just 2 of the included studies failed to meet current best-practice recommendations (Table 3), it is evident that a comprehensive IPP that meets the minimum recommendations is likely necessary to reduce ACL injury risk (Figure 3). Our results also indicate that it may be imperative to include plyometrics, strengthening, and agility exercises in ACL IPPs as these components were common to all the IPPs analyzed except for 1 using only balance exercises that did not protect against ACL injury.[40] Therefore, although our findings generally support current best-practice recommendations,[34] we provide novel evidence that suggests the necessary inclusion of plyometrics, strengthening, and agility exercises into efficacious ACL IPPs.

Finally, despite the lack of significant heterogeneity in the protective effect of the 8 IPPs included in this meta-analysis, we did identify substantial variability in the actual exercises included in each IPP and the method of delivery (Table 3). For example, although lower extremity strengthening, plyometrics, and agility tended to be emphasized in the various IPPs, significant variability was present in the specific exercises that were selected (Table 3). This suggests that as long as the requisite exercise categories are included, clinicians and coaches may have tremendous flexibility when it comes to selecting the specific exercises that their athletes perform. Similarly, although our results also support the notion that providing feedback on proper movement technique is a key ingredient for IPP success (Table 3), a high degree of variability was found regarding how this was achieved. The IPPs included in our analysis tasked coaches,[14,25,39,41,45] sports medicine staff,[14] and/or teammates[32,41] with providing feedback and used video,[14,39] written instructional materials,[14,39-41] and/or training sessions[23,45] to train program participants and/or deliverers. Accordingly, it is likely not necessary for ACL IPPs to be administered by sports medicine professionals as long as the individuals who are tasked with overseeing the IPP have been properly trained. These findings surrounding IPP implementation are especially exciting and encouraging given numerous reports highlighting that efficacious ACL IPPs such as the ones included in our analysis are not being commonly adopted or implemented with high levels of fidelity in the community.[5,7,30,31] Moreover, barriers to widespread high-fidelity IPP implementation in team sports do not center on negative attitudes toward IPPs or a concern about their effectiveness[30] but rather involve a lack of perceived time during practice,[30] inadequate variation and progression offered by current IPPs,[7] and a need to adapt IPPs according to sport, age, or competition level.[7,30] Collectively, our results suggest the potential that ACL IPPs may be able to be "built" locally and collaboratively with stakeholders by selecting specific exercises and a method of delivery that makes sense for the setting as long as the program that is developed meets the overarching framework common to efficacious IPPs identified in this analysis. This type of flexible development and implementation approach—which aligns with many of the recommendations for enhancing the effectiveness and sustainability of an IPP in a real-world setting put forward by Padua et al[35]—would stand in stark contrast to current practice that tends to promote having clinicians or coaches use an ACL IPP as described in an *efficacy* study without consideration for whether that IPP fits the implementation context such that the IPP will be *effective* in the target population.

Limitations and Future Recommendations

Despite the use of ACL IPPs to primarily reduce the risk of noncontact or indirect ACL injuries,[34] our analysis is based on the incidence of total ACL injury due to the small number of studies that have reported noncontact and contact ACL injuries separately. Another limitation of the current study is that by limiting our analysis to the highest quality evidence (RCTs or cluster-RCTs), only 8 studies met our inclusion criteria, with 6 of these studies evaluating soccer exclusively. As such, it is unknown whether the observed 53% reduction in ACL injury rate is generalizable to other sports. Last, current best-practice guidelines recommend that in addition to including activities from at least 3 exercise categories and providing feedback on proper landing mechanics, IPPs should be performed at least 2 or 3 times per week throughout the preseason and in-season.[34] However, rarely was this information or compliance with the IPP reported in the included studies. Thus, we evaluated each IPP based on only its content and whether feedback was provided. Future reviews should seek to address these limitations as additional interventional studies are conducted and published.

CONCLUSION

This meta-analysis addresses 3 key methodological issues found in previous meta-analyses and provides the strongest evidence to date to support that the use of IPPs in team sports can reduce ACL injury risk by 53%. *Efficacious* ACL IPPs tend to include plyometric, strengthening, and agility exercises along with feedback on proper technique. Beyond this, however, we found substantial variability in the specific exercises included in each program and the manner in which the programs were delivered. This suggests that ACL IPPs may be able to be designed or modified within this overarching framework to best meet the specific characteristics of target populations and potentially increase the use of IPPs in team sports. However, although the current investigation provides a strong theoretical underpinning for this flexible approach, future studies will be necessary to test the *effectiveness* of such an approach for increasing IPP adoption and implementation and reducing ACL injury rates.

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