Meta-Analysis of Meta-Analyses of Anterior Cruciate Ligament Injury Reduction Training Programs

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ABSTRACT: Several meta-analyses have been published on the effectiveness of anterior cruciate ligament (ACL) injury prevention training programs to reduce ACL injury risk, with various degrees of risk reduction reported. The purpose of this research was to perform a systematic review and meta-analysis of overlapping meta-analyses evaluating the effectiveness of ACL injury prevention training programs so as to summarize the amount of reduction in risk for all ACL and non-contact ACL injuries into a single source, and determine if there were sex differences in the relative efficacy of ACL injury prevention training programs. Five databases (Medline, PubMed, Embase, CINAHL, and Cochrane) were searched to identify meta-analyses that evaluated the effectiveness of ACL injury prevention training programs on ACL injury risk. ACL injury data were extracted and the results from each meta-analysis were combined using a summary meta-analysis based on odds ratios (OR). Eight meta-analyses met eligibility criteria. Six of the eight only included data for female athletes. Summary meta-analysis showed an overall 50% reduction (OR = 0.5 [0.41–0.59]; $I^2 = 15\%$) in the risk of all ACL injuries in all athletes and a 67% reduction (OR = 0.33 [0.27–0.41]; $I^2 = 15\%$) for non-contact ACL injuries in females. This paper combines all previous meta-analyses into a single source and shows conclusive evidence that ACL injury prevention programs reduce the risk of all ACL injuries by half in all athletes and non-contact ACL injuries by two-thirds in female athletes. There is insufficient data to make conclusions as to the effectiveness of ACL injury prevention programs in male athletes. © 2018 Orthopaedic Research Society. Published by Wiley Periodicals, Inc. J Orthop Res 36:2696–2708, 2018.

Keywords: anterior cruciate ligament; injury prevention; neuromuscular training; sports injury

Anterior cruciate ligament (ACL) rupture is a devastating knee injury that commonly occurs during participation in high impact landing and twisting sports. ACL injury represents a significant financial burden in terms of rehabilitative and surgical costs, as well as the personal cost to the athlete due to absence from sport, and the impact this may have on health and wellbeing.[1,2] Therefore, ACL injury prevention training programs have received considerable attention since their inception two decades ago.

The aim of ACL injury prevention training programs is to influence the neuromuscular system via a combination of plyometrics, strengthening and other neuromuscular training exercises, as well as technique and balance training, to prevent subsequent injury.[3] The efficacy of these programs has been evaluated and generally supported, particularly in female athletes who have a greater relative risk of ACL injury compared with males playing similar sports.[4–6] However, despite the availability of such prevention programs, ACL injury rates appear to be on the increase and it is of concern that recent reports show the rates of ACL injury to have grown most rapidly at the younger end of the age spectrum.[7–9] Therefore, it is timely to revisit the efficacy of ACL injury prevention training programs and critically evaluate the state of the current evidence for their effectiveness.

A large number of literature and narrative reviews have been conducted in order to summarize the evidence for the efficacy of ACL prevention training programs.[10–12] These vary greatly in terms of scope and quality. Systematic reviews performed with use of meta-analyses are a valid means for summarization of the combined results of multiple intervention studies, and have gained acceptance because they are a single source of up-to-date information for the health care provider to make an evidence based practice decision.[13] A number of reviews with meta-analyses have been conducted to evaluate the effectiveness of ACL prevention training programs over the past decade.[3,14–20] However, these reviews have differed in terms of their inclusion of only female athletes in some reviews and athletes of mixed sex in others. In addition, the primary outcome of ACL injury incidence has been reported differently between reviews; some studies reported all ACL injuries and others reported only non-contact ACL injuries, which led to mixed results in terms of efficacy with reduction in risk varying from 39% to 71%. Because the objective of these reviews was to provide the reader with easily accessible high-quality information, the quality of these reviews also needs to be evaluated before the conclusions or recommendations can be properly considered.

It has been estimated that 11 systematic reviews are published every day,[21] making it a challenge to keep up to date even when resorting to systematic reviews. Therefore, overviews, or reviews of reviews, have recently gained interest as a new type of synthesis.[22,23] These compare and combine the findings of several reviews and provide an overall summary in one accessible source. To our knowledge, there has

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been no systematic review of overlapping meta-analyses or "meta-analysis of meta-analyses" that has investigated the effectiveness of ACL injury prevention training programs, despite the numerous reviews and meta-analyses that have been conducted and the differing degrees of effectiveness which have been reported in previous reviews. The purposes of this study were therefore to: (1) perform a systematic review of overlapping meta-analyses to evaluate the effectiveness of ACL injury prevention training programs to reduce ACL injury risk; (2) summarize the amount of reduction in risk for all ACL and non-contact ACL injuries; and (3) determine if there were sex differences in the relative efficacy of ACL injury prevention training programs.

METHODS

Search Methods

A systematic search of the literature was performed using the following databases: Medline, PubMed, Embase, CINAHL (Cumulative Index to Nursing and Allied Health literature) and Cochrane Database of Systematic reviews. The following search terms were used: [ACL OR anterior cruciate ligament OR knee injury OR sport injury] AND [prevention OR neuromuscular OR training OR agility OR plyometric]. Wildcards were used for "preven*," "inj*"and "neuromusc*," All databases were searched from January 1990 until August 3, 2017, and study type limits were set to reviews or meta-analyses. All retrieved references were downloaded into Endnote software (Version X7; Thomson Reuters) and duplicates removed. The reference lists of all included meta-analyses meeting the eligibility criteria were also subsequently manually searched to ensure that no studies were missed.

Selection of Studies

Studies were included if they were (1) a meta-analysis of randomized controlled trials (RCTs) or prospective cohort studies that evaluated the effectiveness of an ACL injury prevention training program and reported data on the incidence of ACL injuries and (2) written in English. Exclusion criteria were (1) systematic reviews that did not pool data or perform a meta-analysis; (2) narrative reviews or those without a search algorithm or failed to describe how studies were selected for the review; (3) reviews that evaluated a general or sports injury prevention program that was not specific to ACL injury prevention; (4) reviews that included non-training interventions such as education or an external device, that is, bracing; or (5) reviews that did not report ACL injury data. Meta-analyses that only focused on components of training programs (i.e., specific exercises or dosage), compliance, or only one sport were excluded. Eligible studies could include participants of either sex.

The titles of all retrieved papers were reviewed and irrelevant studies omitted (i.e., completely different topic), all remaining titles and abstracts were independently reviewed by the two study authors. If it was not clear whether the inclusion criteria were met from reading just the title and abstract, a full version of the paper was retrieved. If the wording systematic review or meta-analysis was not mentioned in the study title or abstract, but the paper was clearly about an ACL prevention training intervention, the full text of the paper was obtained to confirm that a meta-analysis or pooling of data had not been undertaken. Disagreements were discussed until a consensus was reached.

Data Extraction

The following data were extracted from each included study: Primary author, journal of publication, publication year, conflicts of interest, number and publication dates of primary studies included, inclusion and exclusion criteria, performance of heterogeneity analysis, sample size, patient demographic data, types of sports played, details of ACL intervention training program, ACL injury data, and meta-analysis results. Each meta-analysis was also screened to determine the rationale for repetition of the meta-analysis and the number of possible previous meta-analyses cited relative to the number actually cited.

Comprehensiveness of Reporting

The Quality of Reporting of Meta-analyses (QUOROM) checklist was used to assess the comprehensiveness of reporting in the included meta-analyses.[24] This evaluation is based on 18 categories, with a point awarded for each category when more than half of the criteria are met.

Internal Validity (Methodological Quality)

The internal validity of the meta-analyses was assessed by the Assessment of Multiple Systematic Reviews (AMSTAR) method.[25] AMSTAR is an 11-item tool for measurement of the quality of reporting and methodology of systematic reviews. It has demonstrated good reliability and validity,[26–28] with a kappa value of 0.7 for interrater individual item agreement and an overall interclass correlation coefficient of 0.84.[28] Both authors completed the QUOROM and AMSTAR systems for all included reviews and discrepancies discussed until consensus was reached.

Degree of Primary Study Overlap

The Corrected Covered Area (CCA) was used as a measure of primary study overlap as per the procedures of Pieper et al.[23] This measure divides the frequency of repeated occurrences of the index (primary) publication in other reviews by the product of index publications and reviews, reduced by the number of index publications. An overlap of >15 is considered high.

Data Pooling

The results of the meta-analyses were combined using a summary meta-analysis model for odds ratios with 95% confidence intervals. For reviews that reported risk ratios or relative risk reduction, the data were converted to an odds ratio based on the primary data included in the review. For studies that already reported odds ratios, the meta-analysis results were used exactly as reported in the manuscript. This analysis was performed for all female ACL injuries and female non-contact ACL injuries using StatsDirect software (V2.8; Altrincham, UK).

RESULTS

Initially 1,557 studies were retrieved by the electronic database search; none were identified from the manual search of reference lists and relevant journals. After 583 duplicates were removed, 974 articles remained as the total yield. By screening titles and abstracts 886 irrelevant articles were excluded, and the full text of the remaining 88 articles was downloaded for detailed assessment. Of these 80 were excluded (refer to Appendix), and 8 meta-analyses were included in the review.[3,14–20] The search process and exclusion reasons are described in Figure 1.

The characteristics of the included meta-analyses are detailed in Table 1. The studies were published between 2006 and 2015. Six of the meta-analyses included only female participants.[3,14,15,17,18,20]

Authors' Assessment of Prior Meta-Analysis Literature

Authors of four of the eight meta-analyses cited all of the previously published meta-analyses (two of these had no prior studies available to cite) (Table 2). Multiple reasons were cited for repeating the meta-analysis including repeating previous analyses to include the most recent studies, varying inclusion criteria and conducting different data analysis methods. Two of the reviews also sought to address the influence of age[18] and the training duration[20] of the prevention programs as a primary aim; however, both also included the overall effectiveness of the program.

Search Methodology and Primary Study Overlap

Every included study used Medline/PubMed as part of the literature search, and all but one study also used CINHAL (Table 3). There was variation in the utilization of other databases but every study used at least two electronic databases for searching.

There were 17 primary studies included in the various reviews with a minimum of 5 and maximum of 14 studies used in the meta-analyses (Table 4). There was one non-English study,[29] a small pilot study in male athletes, which was cited in one review.[16] There was consistency in which primary studies were included with most of the reviews simply adding more recently published studies. The main difference in primary study inclusion was whether the review included either male and female participants, or females only; and whether all ACL injuries or only non-contact injuries were analyzed. There was substantial overlap between the included primary studies and the CCA score was 54%.

Study Reporting and Quality Assessment (Validity)

QUOROM scores were relatively similar between the reviews and overall indicated satisfactory reporting (Table 5). AMSTAR scores showed that studies uniformly detailed the characteristics of the included studies and most performed a comprehensive literature search and assessed the methodology of included studies and publication bias. No study had a priori published research objectives and rarely did quality factor into decision-making relative to conclusions and recommendations (Table 5).

Only two of the reviews excluded primary studies from the meta-analysis.[16,19] Of these one[16] excluded a primary study due to high attrition rates,[30] this study was included in six of the reviews. The other review[19] excluded two studies that contributed significantly to heterogeneity,[31,32] and two that had no ACL injuries in either the control or intervention groups.[33,34] Some of the primary studies contained data collected over multiple seasons and the meta-analyses were mixed in terms of how these data from multiple seasons were

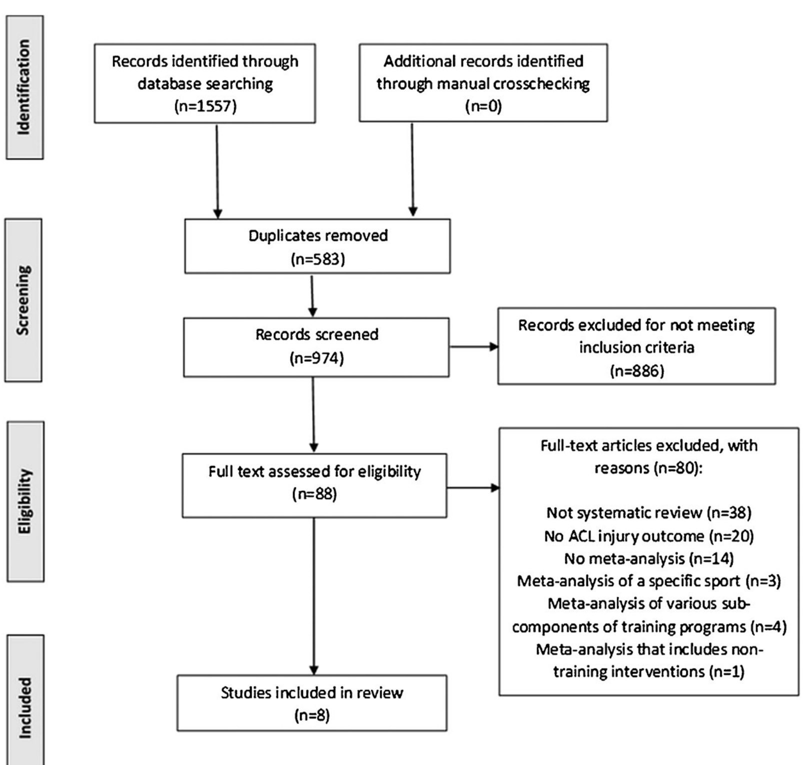

Figure 1. PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram for inclusion of studies.

Table 1. Characteristics of Included Studies

Authors	Journal	Publication Year	Range of Years of Included Studies	No. of Primary Studies	No. of Included RCTs
Hewett et al.[14]	American Journal of Sports Medicine	2006	1999–2005	6	2
Grindstaff et al.[3]	Journal of Athletic Training	2006	1999–2005	5	1
Yoo et al.[15]	Knee Surgery Sports Traumatology & Arthroscopy	2010	1999–2006	7	2
Sugimoto et al.[17]	British Journal of Sports Medicine	2012	1999–2011	12	6
Sadoghi et al.[16]	Journal Bone Joint Surgery (Am)	2012	1996–2008	8[a]	2
Myer et al.[18]	American Journal of Sports Medicine	2013	1999–2012	14	8
Taylor et al.[20]	British Journal of Sports Medicine	2015	1999–2012	13	7
Donnell-Fink et al.[19]	PLoS ONE	2015	1996–2013	16[a]	8

RCT, randomized controlled trial, and included cluster randomization. [a]Not all studies were included in the meta-analysis.

dealt with; some studies included all available seasons and others only the first season to reduce the occurrence of repeat players. Only four studies[3,15–17] included the actual raw numbers of ACL injuries and sample sizes they used to base their meta-analyses calculations.

Study Results and Summary Meta-Analysis

All of the meta-analyses showed a significant effect in favor of the ACL injury prevention training intervention (Table 6). Five of the reviews calculated odds ratios or relative risk,[14–16,18,20] two relative risk reduction together with number need to treat calculations,[3,17] and one calculated incidence risk ratio that took athletic exposure time into account.[19] One of the studies that reported odds ratios calculated these based on both athletic exposures and player seasons.[20] Seven of the eight reviews reported between 39 and 62% reductions in the risk for all ACL injuries (or did not specify mechanism).[14–20] More recently published reviews tended to show a smaller effect. The summary meta-analysis of the meta-analyses, for all ACL injuries, demonstrated a 50% reduction (OR = 0.5 [0.41–0.59]; $I^2 = 15\%$) in the risk of all ACL injuries in all athletes (Fig. 2).

Four of the reviews reported between 64% and 73% reductions in non-contact ACL injury risk, of which only females were included in the analysis.[3,15,17,20] The summary meta-analysis for non-contact ACL injuries demonstrated a 67% reduction (OR = 0.33 [0.27–0.41]; $I^2 = 15\%$) in the risk of non-contact ACL injuries in females (Fig. 3).

Table 2. Number of Meta-Analyses Actually Cited Compared With Maximum Number That Could Be Cited

Authors	Date of Publication, mo/yr[a]	Date of Last Literature Search, mo/yr	No. of Meta-Analyses Possible to Cite	No. of Meta-Analyses Cited
Hewett et al.[14]	03/2006	??/2004	0	N/A
Grindstaff et al.[3]	12/2006	10/2005	0	N/A
Yoo et al.[15]	06/2010	07/2007	2	2
Sadoghi et al.[16]	05/2012	12/2010	3	0
Sugimoto et al.[17]	06/2012[a]	12/2011	3	3
Myer et al.[18]	01/2013	05/2012	5	3
Taylor et al.[20]	08/2013[a]	7/2012	5	4
Donnell-Fink et al.[19]	12/2015	12/2014	7	3

[a]Online publication date.

Table 3. Search Methodology Used by Each Included Study

Authors	Year of Publication	Medline/ PubMed	Embase	Cochrane Library	CINAHL	Other	Language Limitations
Hewett et al.[14]	2006	+			+		Yes
Grindstaff et al.[3]	2006	+			+	+	Yes
Yoo et al.[15]	2010	+		+			Yes
Sadoghi et al.[16]	2012	+	+	+	+		No
Sugimoto et al.[17]	2012	+			+	+	Yes
Myer et al.[18]	2013	+			+	+	Yes
Taylor et al.[20]	2015	+		+	+	+	Yes
Donnell-Fink et al.[19]	2015	+	+	+	+		Yes

DISCUSSION

The purpose of this study was to systematically compile the evidence from multiple meta-analyses on the effectiveness of ACL injury prevention training programs into one accessible up-to-date source. Eight meta-analyses were identified and included in the review.[3,14–20] Six of the eight only included data for female athletes.[3,14,15,17,18,20] From the available evidence, the consistent finding from all eight meta-analyses was that ACL prevention training programs significantly reduced the risk of all ACL injuries and non-contact ACL injuries. The primary difference between the meta-analyses was in the amount of risk reduction. Combination of the results of the meta-analyses showed an overall 50% reduction in the risk for all ACL injuries in all athletes and 67% reduction for non-contact ACL injuries in females. These are substantial, clinically significant reductions and confirm the benefit of such interventions.

As health providers typically access such meta-analyses for high quality information, it is important that the quality of these reviews is evaluated and that

Table 4. Citation Matrix of Primary Studies Included in the Review and Meta-Analysis

Primary Study	Hewett et al.[14]	Grindstaff et al.[3]	Yoo et al.[15]	Sadoghi et al.[16]	Sugimoto et al.[17]	Myer et al.[18]	Taylor et al.[20]	Donnell-Fink et al.[19]
Caraffa et al.[31]				+				‡
Hewett et al.[5]	+	+	+	+	+	+	+	+
Heidt et al.[35]	+		+	+	+	+	+	+
Soderman et al.[30]	+		+	*	+	+	+	+
Petersen et al.[29]				+				
Myklebust et al.[32]	+	+	+		+	+	+	+
Mandelbaum et al.[6]	+	+	+	+	+	+	+	‡
Petersen et al.[36]	+	+	+	+	+	+	+	+
Olsen et al.[37]		+			+	+	+	+
Pfeiffer et al.[38]			+	+	+	+	+	+
Steffen et al.[39]					+	+	+	+
Gilchrist et al.[4]				+	+	+	+	+
Pasanen et al.[40]						+		+
Kiani et al.[34]					+	+	+	#
La Bella et al.[41]					+	+	+	+
Walden et al.[42]						+	+	+
Grooms et al.[33]								#

Removed from meta-analysis due to *high attrition rate; ‡ heterogeneity; # zero injuries in either control or intervention group; + study included in the meta-analysis.

Table 5. AMSTAR Criteria for Included Meta-Analyses and QUOROM Score

Items	Hewett et al.[14]	Grindstaff et al.[3]	Yoo et al.[15]	Sadoghi et al.[16]	Sugimoto et al.[17]	Myer et al.[18]	Taylor et al.[20]	Donnell-Fink et al.[19]
AMSTAR criteria								
Was an "a priori" design provided?	0	0	0	0	0	0	0	0
Was there duplicate selection and data extraction?	0	0	1	1	1	0	1	1
Was a comprehensive literature search performed?	0	1	1	1	0	1	1	1
Was the status of publication used as an inclusion criterion?	0	0	0	0	0	0	0	0
Was a list of included/excluded studies provided?	0	0	0	0	0	0	0	0
Were the profiles of the included studies provided?	1	1	1	1	1	1	1	1
Was the methodological quality of the included studies evaluated and documented?	0	1	0	1	1	1	1	1
Was the specific quality of the included studies used appropriately in formulating conclusions?	0	1	0	1	0	0	0	1
Were the methods used to combine the findings of studies appropriate?	0	0	1	1	0	0	1	1
Was the publication bias evaluated?	0	0	1	1	1	1	1	1
Were the conflicts of interest stated?	1	0	0	1	1	1	1	1
Total AMSTAR score	2	4	5	8	5	5	7	8
QUOROM score	9	16	13	16	16	15	14	14

differences between reviews can be easily determined. The current study provides an overview of such information. Primary sources (i.e., original studies) included in each review are detailed together with the study methodology employed by each of the meta-analyses. The results presented also reflect the consistency of the conclusions in each individual meta-analysis and highlight the necessity of bringing together a summary of the meta-analyses in one overall analysis, which was the goal and is the product of this current analysis.

The current review and analysis showed that there is a robust evidence base in support of the effectiveness of ACL injury prevention training programs for female athletes, but that there is limited information for male athletes. There were only three primary studies that included male participants.[29,31,33] Two of these had a small number of participants (64 and 36 participants in total, respectively)[29,33] and of these two, one was non-English[29] and the other was not able to be included in the meta-analysis as there were no ACL injury events in either the control or intervention groups.[33] Despite these limited data, Sadoghi et al.[16] reported an 85% reduction in relative risk for males in their meta-analysis. Another more recent study has been conducted in male athletes.[43] In this study, a large number of soccer players (675 intervention, 850 control) participated in an ACL injury prevention training program and a 77% reduction in the risk of ACL injury was found. This is an encouraging finding and indicates that the effectiveness of ACL injury prevention training programs in males should be further investigated to confirm the above results, which are based on limited data.

There is no one recommended tool for the measurement of study quality of systematic reviews and meta-analyses. The QUOROM provides a checklist for completeness of study reporting and the AMSTAR score is commonly used for assessment of bias and validity. Both were used in the current review. In terms of reporting, it was perhaps most concerning that only half of the included meta-analyses reported the actual numerical values from which the meta-analyses were based. As there was some inconsistency between the extracted numbers in the reviews which provided this information, it is imperative that these data be made available for transparency and replication. These data were not provided in the most recent reviews.

Table 6. Meta-Analyses Results

Authors	Population	No. Treatment Group	No. Control Group	No. ACL Injuries (Non-Contact) Treatment Group	No. ACL Injuries (Non-Contact) Control Group	Meta-Analysis Results[a]	Direction of Findings
Hewett et al.[14]	Female	3,602	6,346	29 (NR)	110 (NR)	OR = 0.4 [0.26–0.61]	Favors intervention reduced all ACL injury risk by 60%
Grindstaff et al.[3]	Female	4,863	6,163	NR (24)	NR (100)	NNT = 89 [66–136] RRR = 70% [54–80]	Favors intervention reduced non-contact ACL risk by 70%
Yoo et al.[15]	Female	3,999	6,462	34 (NR)	123 (NR)	All ACL injuries: OR = 0.4 [0.24–0.6] Non-contact ACL injuries: OR = 0.36 (0.23–0.54]	Favors intervention reduced all ACL injury risk by 51–60%
Sugimoto et al.[17]	Female	4,192 (All ACL) 8,064 (non-contact)	4,191 (All ACL) 10,019 (non-contact)	45 (27)	80 (126)	All ACL injuries: RRR = 43.8 [28.9–55.5] NNT = 120 [74–316] Non-contact ACL injuries: RRR = 73.4 [62.5–81.1] NNT = 108 [86–150]	Favors intervention reduced all ACL risk by 43.8% and non-contact ACL risk by 73.4%
Sadoghi et al.[16]	Male and female	3,905	6,713	34 (NR)	181 (NR)	RR = 0.38 [0.2–0.72] Female RR = 0.48 [0.26–0.89] Male RR = 0.15 [0.08–0.28]	Favors intervention reduced all ACL injury risk by 62%
Myer et al.[18]	Female	NR	NR	69 (NR)	179 (NR)	OR = 0.54 [0.35–0.83]	Favors intervention reduced all ACL injury risk by 46%
Taylor et al.[20]	Female	11,378	12,810	NR (NR)	NR (NR)	All ACL injuries: OR = 0.61 [0.44–0.86] Non-contact ACL injuries: OR = 0.35 [0.23–0.54][b]	Favors intervention reduced all ACL injury risk by 39% and non-contact ACL risk by 65%
Donnell-Fink et al.[19]	Male and female	NR	NR	NR (NR)	NR (NR)	IRR = 0.493 [0.285–0.854][c]	Favors intervention reduced all ACL injury risk by 50.7%

OR, odds ratio; NR, raw numbers not reported; NNT, number needed to treat; RRR, relative risk reduction; IRR, incidence rate ratio. [a]Unless stated otherwise results are for all ACL injuries in females. [b]OR expressed relative to player seasons. [c]Studies contributing to heterogeneity excluded.

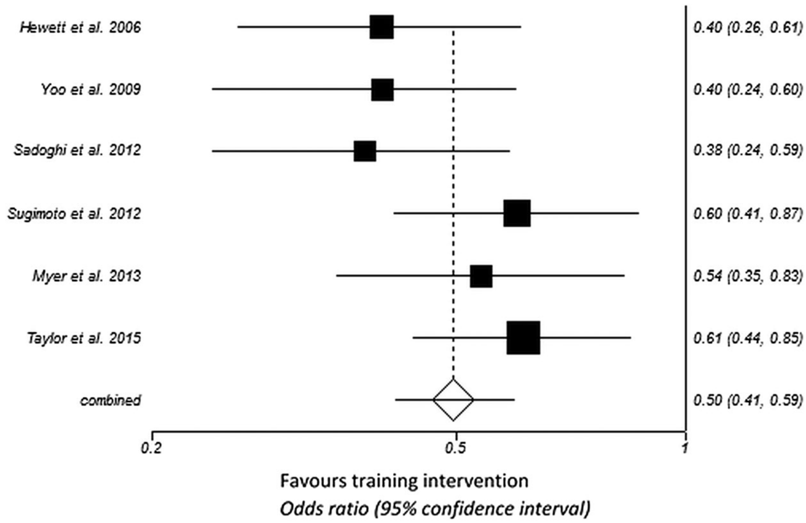

Figure 2. Summary meta-analysis of the meta-analyses for all ACL injuries in all athletes that demonstrated a 50% reduction (OR = 0.5 [0.41–0.59]; $I^2 = 15\%$) in the risk for all ACL injuries.

The scope of the current review was to take a macro approach and evaluate meta-analyses on the effectiveness of an entire ACL prevention training program. There were of course differences in the content and delivery of the interventions themselves and it was not the intent of this review to detail the micro level of the programs. Nonetheless, information from the included reviews indicates that comprehensive programs (i.e., those which include plyometrics, strengthening, and other neuromuscular training exercises)[3,14] may be of greatest benefit, particularly in younger athletes.[18] Compliance is also important and a further meta-analysis has shown significantly greater reductions in ACL injury risk to be associated with greater compliance with the training interventions.[44]

This analysis is not without limitations. One factor which was not addressed by the meta-analyses included in this review is that of the sustained benefit of such prevention programs. The prevention programs were also implemented in the setting of primary ACL injury and their efficacy for secondary ACL injury prevention (both unilateral and contralateral injury) also requires further investigation. Another potential limitation of a meta-analysis of meta-analyses is that many of the primary studies are included in more than one meta-analysis, potentially giving proportional power to studies appearing in multiple reviews.[23] In this review, studies with an earlier publication date were included in more meta-analyses, so may be overrepresented. While this should be kept in mind, it is notable that the most recent meta-analysis by Donnell-Fink et al.,[19] which was not included in the summary meta-analysis because it included both male and female athletes, reported a 51% reduction in risk, which is highly consistent with the current analysis' overall findings.

Another limitation of this meta-analysis and all the meta-analyses and original studies analyzed is their use of the term "Injury Prevention Program." Identification of these meta-analyses would not be possible

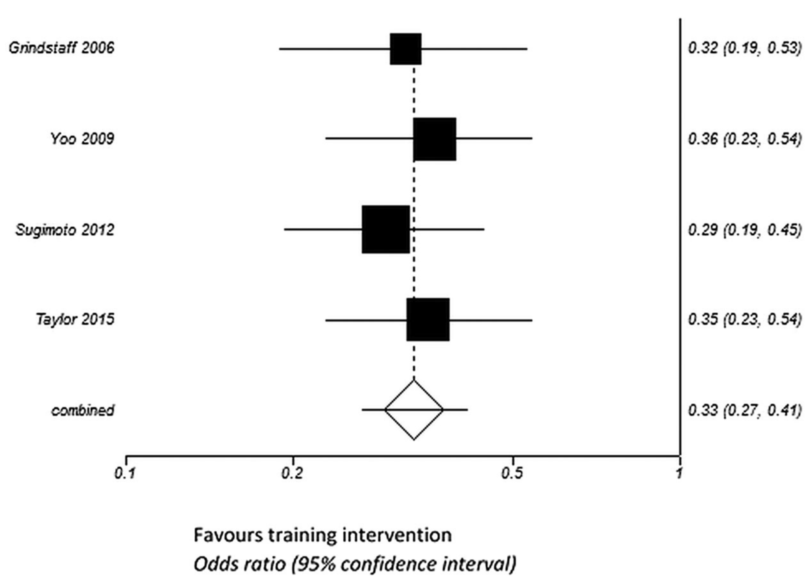

Figure 3. Summary meta-analysis of the meta-analyses for non-contact ACL injuries in females that demonstrated a 67% reduction (OR = 0.33 [0.27–0.41]; $I^2 = 15\%$) in the risk of non-contact ACL injuries.

without the use of the "prevention" search term. However, prevention may be an improper term in this usage for multiple reasons. It implies stopping a specific event from occurring and that's not likely what these programs do. Prevention is the action of stopping something from happening or arising; alternatively, reduction is the action or fact of making a specified thing smaller or less in amount, degree or size. The outcome these studies measure and report that result from a "prevention program" is the amount of risk reduction or change in ACL injury incidence rates post intervention, not prevention. By definition, if we can prevent an ACL injury, then we can predict an ACL injury; however, this concept remains controversial.

This study has several strengths and the approach used is novel for multiple reasons. This is the first systematic review of meta-analyses of ACL injury prevention training programs and the first to combine the meta-analyses into a summary meta-analysis for both all ACL injuries and non-contact ACL injuries. It includes all the available primary evidence, except for a recently published study in male athletes.[43] As such, it represents a comprehensive overview of this topic and critically analyses the previously conducted meta-analyses.

In conclusion, the overall finding of the analysis demonstrated that ACL injury reduction programs decrease the risk of all ACL injuries by half and non-contact ACL injuries in all athletes by two-thirds in female athletes. There is currently insufficient data to make strong conclusions or recommendations as to the effectiveness of ACL injury prevention programs in male athletes. Therefore, future research should continue to assess the effectiveness of such programs in male athletes, whether they have a sustained benefit, and also investigate the potential for the application of these findings for reduction of second ACL injury risk.

AUTHORS' CONTRIBUTIONS

All authors contributed to the design, analyses, and reporting for this manuscript. All authors have read and approved the final submitted manuscript.

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Appendix

Excluded Studies After Full Text Retrieval.

Reason	Study Reference
Not a systematic review ($n = 38$)	47,51,52,54–62,65,67,68,72,74,75,77, 80–87,96,97,100,103,104,106,107, 109–112,119
No ACL injury outcome ($n = 20$)	45,46,50,53,63,64,71,78,79,88–92,95,108, 121–123
No meta-analysis ($n = 14$)	48,49,70,73,76,93,94,98,99,101,102,113,114,124
Meta-analysis of a specific sport only ($n = 3$)	69,105,120
Meta-analysis of various sub-components or compliance of training program ($n = 4$)	115–118
Meta-analysis that includes non-training intervention ($n = 1$)	66