The Influence of Age on the Effectiveness of Neuromuscular Training to Reduce Anterior Cruciate Ligament Injury in Female Athletes

CME

A Meta-Analysis

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Background: In female athletes, sports-related injuries to the anterior cruciate ligament (ACL) increase during adolescence and peak in incidence during the mid- to late teens. Although biomechanical investigations indicate that a potential window of opportunity exists for optimal timing for the initiation of integrative neuromuscular training (NMT) in young female athletes, the influence of the timing of initiation of these programs on the efficacy of ACL injury reduction has yet to be evaluated.

Hypothesis/Purpose: The purpose of the current report was to systematically review and synthesize the scientific literature regarding the influence of age of NMT implementation on the effectiveness for reduction of ACL injury incidence. The hypothesis tested was that NMT would show a greater effect in younger populations.

Study Design: Meta-analysis; Level of evidence 1a.

Methods: Data were pooled from 14 clinical trials that met the inclusion criteria of (1) number of ACL injuries reported; (2) NMT program used; (3) female participants were included; (4) investigations used prospective, controlled trials; and (5) age of participants was documented or was obtainable upon contact with the authors. A meta-analysis with odds ratio (OR) was used to compare the ratios of ACL injuries between intervention and control groups among differing age categorizations.

Results: A meta-analysis of the 14 included studies demonstrated significantly greater knee injury reduction in female athletes who were categorized in the preventive NMT group compared with those who were in the control group (OR: 0.54; 95% confidence interval [CI]: 0.35, 0.83). Lower ACL injuries in mid-teens (OR 0.28; CI: 0.18, 0.42) compared with late teens (OR 0.48; CI: 0.21, 1.07) and early adults (OR 1.01; CI: 0.62, 1.64) were found in participants undergoing NMT.

Conclusion: The findings of this meta-analysis revealed an age-related association between NMT implementation and reduction of ACL incidence. Both biomechanical and the current epidemiological data indicate that the potential window of opportunity for optimized ACL injury risk reduction may be before the onset of neuromuscular deficits and peak knee injury incidence in female athletes. Specifically, it may be optimal to initiate integrative NMT programs during early adolescence, before the period of altered mechanics that increase injury risk.

Keywords: anterior cruciate ligament injury risk factors; targeted neuromuscular training; knee injury prevention; youth injury prevention; STOP sports injuries

Epidemiological studies have demonstrated that in landing and cutting/pivoting sports, injury to the anterior cruciate ligament (ACL) occurs at a 4- to 6-fold greater incidence in female athletes when compared with male athletes.[2] The large sex disparity in ACL injury incidence has increased public awareness and fueled many mechanistic and interventional investigations to determine sex-specific responses to prevention strategies. In the past 25 years, study of this important knee-stabilizing ligament has resulted in nearly 10,000 scientific articles indexed on Medline.[53] However, despite the many scientific advances in the treatment of ACL injury, and regardless of the treatment strategy (nonoperative management versus operative treatment), osteoarthritis (OA) occurs at 10 times the normal rate in ACL-injured patients.[15]

From the vast scientific evidence related to ACL injury in female patients, several theories have emerged to explain the sex disparity in knee injury risk that include sex-specific hormonal and anatomic variances, along with associated sex disparities in neuromuscular abilities.[1,27] There have been many investigations of the connection

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between hormonal involvement and injury; however, results have not been conclusive on exactly how hormones play a role in the increased risk of injury in women.[32,71] Anatomic differences between men and women have also been explored relative to their potential contribution to increased injury incidence in women.[1,27] Unfortunately, the data linking anatomic measures to injury incidence are equivocal, and the extent to which these factors may be modified limits the relative importance of research in these arenas. Conversely, mechanistic investigations of injury have identified altered neuromuscular strategies during the execution of sports movements in female athletes that likely underlie their increased risk of ACL injury in relation to injury risk in male athletes in similar sports.[8,17,18,30,38,51] Prospective measures of dynamic knee valgus during landing in young female athletes at risk for ACL injury and related knee postures are commonly reported mechanisms of injury.[5,30,57] In addition, a large-scale prospective study found similar results of increased valgus alignment during the landing phase of a drop vertical jump in military cadets who sustained ACL injury (Padua DA, Marshall SW, Beutler AI, Garrett WE, "Prospective Cohort Study of Biomechanical Risk Factors of ACL Injury: The JUMP-ACL Study." Paper presented at the American Orthopaedic Society of Sports Medicine, 2009). Importantly, these noted biomechanical risk factors are sensitive to modification with neuromuscular training (NMT) interventions.[31,35,46,47,51,52]

Interestingly, there has not been significant evidence of this sex difference in injury incidence or altered biomechanics in prepubertal female athletes, but only postpubertal female athletes. These findings indicate that through the pubertal transformation during the adolescent years, boys and girls diverge from one another in development, inherently putting female athletes at greater risk of a devastating injury such as a rupture of the ACL in the postpubertal years. It is noted that although hormonal and anatomic changes take place in the pubertal transition, these alterations are not modifiable, which presents difficulty in addressing these factors to prevent injury.[1,27] From a different perspective, power/strength and coordination have been shown to increase with puberty in boys; however, the same changes have not been observed in girls.[4] Altered mechanics associated with increased risk of injury in female athletes emerge after the pubertal growth spurt,[30,48] and they appear to coincide with peak prevalence of ACL injury.[16,19,24,28,48] Interestingly, these different landing strategies include landing with the knee in a more valgus position and with less overall control of the lower extremity, putting the ACL at high risk for being injured in this postpubertal female population. This absence of neuromuscular control may be the underlying cause of increased risk of injury in postpubertal female athletes, however, the reason that female athletes lack the ability to maintain proper landing alignment may be linked to hip abductor strength and trunk stability.[26] Both of these variables are modifiable through the proper neuromuscular intervention, which focuses on improvement of the ability to maintain proper landing mechanics through increasing hip strength and decreasing lateral trunk motion by improving control of the core musculature.[39,42,47] Based on these results, several NMT protocols have emerged in the literature that target ACL injury prevention in female athletes.[**]

Emergent youth sport participation has significantly increased over the past decade, and these athletes are also starting participation at a younger age,[56] which may place them at a greater risk of injury if they do not possess the adequate strength and proper conditioning to prevent devastating injuries.[45] The 2008 Physical Activity Guidelines for Americans, issued by the US Department of Health and Human Services, recommend for children and young adolescents aged 6 to 17 years to include "muscle- and bone-strengthening" exercises into their exercise regimens.[65] This report, in turn, raised concern over the proper age and method to implement NMT programs in this youth population. Although it may be suggested that initiating this type of program in youth and adolescents is conducive to the prevention of injury, the question remains whether NMT to prevent ACL injuries is best implemented at a certain time in a young athlete's career.[44,45] Therefore, the purpose of the current investigation was to systematically review and synthesize the scientific literature in regard to the influence of age of NMT implementation on the effectiveness for reduction of ACL injury incidence in female athletes. The hypothesis tested was that NMT would show greater efficacy in younger populations.

METHODS

Literature Search

A literature search was performed using the PubMed and EBSCO host (CINAHL, Medline, SPORTDiscus) from 1995 to May 31, 2012. The keyword search was performed by applying a combination of following words: "knee," "anterior cruciate ligament," "ACL," "prospective," "neuromuscular," "training," "female," and "prevention." Language was limited to English, and subjects were all human. The following inclusion criteria were applied: (1) the number of ACL injury

**References 21, 22, 25, 33, 34, 37, 55, 58, 60-62, 66, 67, 70.

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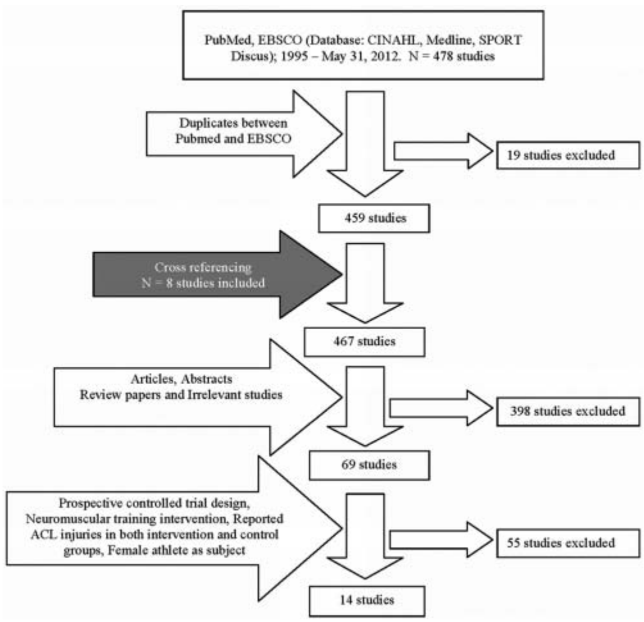

Figure 1. Flow chart of literature review.

incidents were reported, (2) an NMT intervention that aimed to reduce ACL incidence was applied, (3) a control group was used, (4) a prospective controlled trial study design was employed, and (5) female patients were included. Abstracts, posters, and unpublished data were excluded (Figure 1). During this process, a potential inclusion of studies that hold very similar characteristics of the above inclusionary criteria were discussed among authors. The Egger regression was used to examine a potential risk of publication bias.

Quality of Methodology Evaluation Method

The Physiotherapy Evidence Database (PEDro) scale was used to analyze methodological quality of the included investigations. The PEDro scale is a widely used measurement tool to rate the methodological quality of the randomized clinical intervention trials. Two reviewers independently examined the methodological quality of each study with the PEDro scale. Discrepancies between reviewers were settled by arbitration and consensus.

Level of Evidence and Strength of Recommendation Assessment Method

To evaluate the quality of the current analysis, the Centre for Evidence-based Medicine (CEBM) level of evidence was implemented. The CEBM level of evidence is used to assess the research design quality of the included investigations and to facilitate the generation of a grade of strength of recommendation for the current analyses.

Data Extraction

The number of incidents of ACL injury in each group (control and intervention), the number of athletes in each group (control and intervention), and the age of the subjects (mean or ranged data) were extracted from each study. Whether or not the ACL incidences were contact or noncontact in nature was also extracted from each study's data. When the mechanism of injury was not documented as either contact or noncontact, an email was sent to the corresponding author listed in the original paper; the email asked the nature of each of the ACL injuries reported in the authors' investigations. Similarly, when neither mean nor range of the participants' ages was recorded, contact was made through email to the corresponding authors. From investigations that had both male and female subjects, only data regarding female subjects were included.

In the literature search using the PubMed and EBSCO keyword search, 467 publications were found, including cross-referenced studies (Figure 1). Among them, 14 investigations met the inclusion criteria of the current analyses (Figure 1).[††] The NMT components of each study, as well as observed numbers of ACL injuries, are summarized in Table 1. The relevant methodological quality as evaluated by the PEDro scores is presented in Table 2. The mean PEDro score was 4.8/10 for the 14 reviewed investigations. Four investigations were rated as high as 7/10,[58,60,67,70] whereas 2 studies were classified 2/10 by PEDro score.[61,62]

Data Analysis

To determine NMT effectiveness, a meta-analysis with 95% confidence interval (CI) was employed. A meta-analysis is capable of synthesizing NMT's effectiveness on the incidence of ACL injury, which was extracted from the included studies and expressed as a summary effect. Because it was assumed that effect size of each study is different, a random-effects model was chosen for the current meta-analysis. To compare a ratio of ACL injuries in subjects between intervention and control groups, odds ratio (OR) was used. Forest plots and the Egger regression were used to examine potential risk of publication bias assessment.

In addition, the incidence of ACL injury was analyzed based on the subjects' mean age and range data. The incidence of ACL injury was classified by subjects' age: either $\leq$18 years or $>$18 years. The dichotomized age categorizations (age $\leq$18 vs $>$18 y) were chosen because subjects in more than half of the reviewed studies were categorized as younger than 18 years old.[‡‡] Subsequently, the incidence of ACL injury was further broken down into 3 age categories: midteens (14-18 y), late teens (18-20 y), and early adults (older than 20 y). This tertile categorization was performed to further evaluate effect of NMT on specific age categorizations.

SUMMARIES OF INCLUDED STUDIES

Hewett et al, 1999
(PEDro Score 3, Level of Evidence 2b)

This research team used a prospective cluster trial design and provided 6 weeks of NMT, which consisted of plyometrics, weight training, and flexibility. Each NMT session

[††]References 21, 22, 25, 33, 34, 37, 55, 58, 60-62, 66, 67, 70.
[‡‡]References 22, 25, 33, 34, 37, 58, 62, 67.

TABLE 1
Summary of Reviewed Studies Including Study Design, Level of Evidence, Sports, Number of Teams, Ages, Training Modes, and Number of ACL Injuries[a]

Study (Year)	Study Design	Level of Evidence	Sports	No. of Teams	Age, y	Training Modes	No. of ACL Injuries
Hewett et al[25] (1999)	Prospective nonrandomized cohort	2b	Soccer, volleyball, basketball	Control: 15 teams Intervention: 15 teams	14-18 (range)	Stretching, plyometrics, weight training	Control: 5 Intervention: 2
Soderman et al[67,b] (2000)	Prospective randomized control	2b	Soccer	Control: 6 teams Intervention: 7 teams	Control: 20.5 ± 5.4 Intervention: 20.4 ± 4.6 (mean ± SD)	Balance with balance boards	Control: 1 Intervention: 4
Heidt et al[22] (2000)	Prospective randomized control	1b	Soccer	Control: 258 subjects Intervention: 42 subjects	14-18 (range)	Cardiovascular, plyometrics, strength, flexibility, agility, and sports specific drills	Control: 8 Intervention: 1
Myklebust et al[55,c] (2003)	Prospective nonrandomized crossover	2b	Handball	1st year: 60 teams 2nd year: 58 teams	21-22 (mean)	Balance with mats and wobble boards	Control: 29 Intervention: 23
Mandelbaum et al[37] (2005)	Prospective nonrandomized cohort	2b	Soccer	Control: 207 teams Intervention: 97 teams	14-18 (range)	Basic warm-up, stretching, strengthening, plyometrics, and agility	Control: 67 Intervention: 6
Olsen et al[58] (2005)	Prospective cluster randomized controlled	1b	Handball	Control: 59 teams Intervention: 61 teams	15-17 (range)	Warm-up, technique, balance, strength, and power	Control: 9 Intervention: 3
Petersen et al[61,d] (2005)	Prospective matched cohort	2b	Handball	Control: 10 teams Intervention: 10 teams	Control: 19.8 Intervention: 19.4 (mean)	Education, balance-board exercise, jump training	Control: 5 Intervention: 1
Pfeiffer et al[62] (2006)	Prospective nonrandomized cohort	2b	Soccer, volleyball, basketball	Control: 69 teams Intervention: 43 teams	14-18 (range)	Plyometrics	Control: 3 Intervention: 3
Steffen et al[67] (2008)	Prospective cluster randomized controlled	1b	Soccer	Control: 51 teams Intervention: 58 teams	15.4 (mean)	Core stability, balance, plyometrics	Control: 5 Intervention: 4
Gilchrist et al[20] (2008)	Prospective cluster randomized controlled	1b	Soccer	Control: 35 teams Intervention: 26 teams	Control: 19.9 Intervention: 19.9 (mean)	Basic warm-up, stretching, strengthening, plyometrics, and agility	Control: 18 Intervention: 7
Pasanen et al[60] (2008)	Prospective cluster randomized controlled	1b	Floorball	Control: 14 teams Intervention: 14 teams	24 (mean)	Running techniques, balance and body control, plyometrics, strengthening	Control: 4 Intervention: 6
Kiani et al[33,e] (2010)	Prospective cluster nonrandomized cohort	2b	Soccer	Control: 49 teams Intervention: 48 teams	Control: 15.0 Intervention: 14.7 (mean)	Core strengthening, balance	Control: 5 Intervention: 0
LaBella et al[34] (2011)	Prospective cluster randomized controlled	1b	Soccer, basketball	Control: 53 teams Intervention: 53 teams	Control: 16.2 Intervention: 16.2 (mean)	Strengthening, plyometrics, balance, agility	Control: 6 Intervention: 2
Walden et al[70] (2012)	Prospective cluster randomized controlled	1b	Soccer	Control: 109 teams Intervention: 121 teams	Control: 14.1 Intervention: 14.0 (mean)	Core stability, balance, jump-landing with knee alignment feedback	Control: 14 Intervention: 7

[a]Control, control group; Intervention, intervention group.
[b]Although the study was a randomized controlled design, the follow-up rate was low (51.2%). Therefore, the level of evidence was rated as 2b.
[c]For the purpose of analysis, data from only the first intervention year were used.
[d]Although there was no specific statement, the neuromuscular training indicated plyometric components.
[e]Although there were jump-landing maneuvers, repeated stretch-shortening cycles were not employed in the training.

lasted 60 to 90 minutes and took place 3 times per week. Athletic trainers and physical therapists gave instructions for the stretching, resistance training, and plyometric techniques while demonstrating proper form, and the plyometric training sessions progressed through 3 phases: (1) technique phase, (2) fundamental phase, and (3) performance phase. The 15 girls' teams that received the intervention consisted of 366 athletes: 185 volleyball (50.5%), 97 soccer (26.5%), and 84 basketball (23.0%) players. There was no age information on the original manuscript; however, the subjects' age

TABLE 2
PEDro Scores of the Reviewed Studies[a]

Reviewed Study (year)	Total Score	PEDro Scale										
		1	2	3	4	5	6	7	8	9	10	11
Hewett et al[25] (1999)	3	—							X	X	X	
Soderman et al[67,b] (2000)	4	—	X		X						X	X
Heidt et al[22] (2000)	5	—	X					X	X	X	X	
Myklebust et al[55,b] (2003)	5	—						X	X	X	X	X
Mandelbaum et al[37] (2005)	3	—							X		X	X
Olsen et al[58] (2005)	7	—	X		X			X	X	X	X	X
Petersen et al[61,b] (2005)	2	—									X	X
Pfeiffer et al[62] (2006)	2	—									X	X
Steffen et al[67] (2008)	7	—	X	X				X	X	X	X	X
Gilchrist et al[20] (2008)	4	—	X		X						X	X
Pasanen et al[60] (2008)	8	—	X	X	X			X	X	X	X	X
Kiani et al[33,b] (2010)	4	—			X			X			X	X
LaBella et al[34] (2011)	6	—	X	X					X	X	X	X
Walden et al[70] (2012)	7	—	X	X	X			X		X	X	X

[a]Note: X indicates a "yes" score. Blank indicates a "no" score. PEDro scale is optimized for evaluation of randomized control trails, thus the PEDro assessment score for the nonrandomized control should be interpreted with caution. 1, eligibility criteria specified; 2, random allocation of subjects; 3, allocation concealed; 4, similar groups at baseline; 5, blinding of subjects; 6, blinding of intervention providers; 7, blinding of outcome assessors; 8, outcomes obtained from 85% of subjects; 9, use of intent-to-treat analysis if protocol violated; 10, between-group statistical comparison; 11, point measures and measures of variability.
[b]Not randomized trials.

range, which was 14 to 18 years old, was confirmed by a corresponding author upon contact.

Soderman et al, 2000 (PEDro Score 4, Level of Evidence 2b)

This prospective randomized controlled trial provided 10 to 15 minutes of balance training using dynadiscs and balance boards. One hundred twenty-one athletes (7 teams) were assigned to the intervention group and 100 athletes (6 teams) were assigned to the control group. The athletes in the intervention group received a special training in initiation of the training and asked to perform the balance training with balance boards every day for the first month at home. After the first month, the home balance training was decreased to 3 days per week. The subjects' mean age was 20.4 years old for the intervention group and 20.5 years old for the control group.

Heidt et al, 2000 (PEDro Score 5, Level of Evidence 1b)

This research group employed a 75-minute-long, custom-made speed and agility program in 42 randomly selected high school–age soccer players for a total of 21 sessions (first session is an orientation) over 7 weeks. The randomly selected subjects in the intervention group commuted to a local gym to perform the intervention program during the preseason. Supervision and feedback was given to recognize and avoid faulty movements. In this study, the subjects' ages ranged from 14 to 18 years old.

Myklebust et al, 2003 (PEDro Score 5, Level of Evidence 2b)

A 3-year prospective crossover trial (the first year was an observational year, whereas the 2 subsequent years were intervention periods) recruited 1705 female handball players playing for the top 3 Norwegian handball leagues. A 15-minute session of balance exercises with mats and wobble boards was implemented 3 days per week in the initial 5 to 7 weeks and was subsequently reduced to once a week for the remainder of the handball season (approximately 5 months). During the second intervention year, a physical therapist was assigned to each team to supervise the given intervention. No age information was found in the original manuscript. However, a corresponding author verified that the subjects' ages were 21 or 22 years old.

Mandelbaum et al, 2005 (PEDro Score 3, Level of Evidence 2b)

Using a prospective cluster cohort trial design, the research team applied a neuromuscular and proprioceptive program called "Prevent Injury and Enhance Performance" (PEP) program to 1885 female soccer players (1041 subjects in the first year and 844 in the second year) and compared the number of ACL injuries to age- and skill-matched controls. The PEP is a 20-minute-long program that prescribed 2 or 3 sessions per week consisting of education, basic warm-up, stretching and strengthening for the trunk and lower extremities, and plyometrics. Coaches for the intervention teams attended a mandatory league meeting during which the PEP program was introduced and they were educated on how to instruct each activity with proper biomechanical technique. They were also provided with a supplemental videotape to help facilitate proper techniques throughout the program, which provided visual examples of proper and improper biomechanical performances for each exercise. In this study, the subjects' age range was between 14 to 18 years old.

Olsen et al, 2005 (PEDro Score 7, Level of Evidence 1b)

With cluster-randomized controlled trial design, a 15- to 20-minute-long structured warm-up program was implemented to aim awareness of neuromuscular control, balance, plyometrics, and strength of knees and ankles in running, cutting, and landing techniques in Norwegian handball players (808 subjects in the intervention group). The structured warm-up program had 4 different types of exercises (warm-up, technique, balance, and strength/power), and each of the exercises was designed to increase the level of difficulty. To ensure the quality of the warm-up program, a trained instructor followed up with each team several times during the season. The structured warm-up program was performed in 15 consecutive sessions and then once a week during 1 competitive Norwegian handball season. The subjects in this study were 15 to 17 years old.

Petersen et al, 2005 (PEDro Score 2, Level of Evidence 2b)

A prospective cohort study incorporated 10 minutes of injury-prevention training into a team warm-up. The injury-prevention training program consisted of education for injury mechanism awareness and prevention strategies, balance-board exercises, and jump training. The program was executed 3 times per week and once a week during the competition period. Coaches and players were informed about the mechanisms of lower extremity injuries (ankle and ACL) and the position of the leg that puts the ACL at risk. The players were also instructed on techniques to reduce injury risk during high-risk activities. Lower extremity injuries were tracked in 134 female handball players who performed the training program and compared with age- and skill-matched controls. Age information was not found in the original manuscript. After an email contact, a corresponding author provided the subjects' mean age, which was 19.4 years in the intervention group and 19.8 years in the control group.

Pfeiffer et al, 2006 (PEDro Score 2, Level of Evidence 2b)

This research team implemented a 20-minute, plyometric-based exercise program twice a week in high school female soccer, volleyball, and basketball athletes for 2 years. The plyometric-based exercise program, "Knee Ligament Injury Prevention" (KLIP), was developed by various health care practitioners, and all of the teams that participated in the treatment group received instruction on how to implement the KLIP program. In addition, teams were provided an instructional videotape and printed handouts of the program, and author correspondence indicated that a trained instructor demonstrated correct form of the plyometric exercises to the subjects in the intervention group. In total, 577 athletes (43 teams) were categorized in the intervention group and 862 athletes (69 teams) were categorized in the control group. Because the age information was not available in the original manuscript, contact was made with a corresponding author, who confirmed the subjects' age range as 14 to 18 years.

Pasanen et al, 2008 (PEDro Score 8, Level of Evidence 1b)

This cluster-randomized controlled study provided 20 to 30 minutes of NMT to top-level floorball athletes several times during the 6-month season. The NMT was designed to enhance athletes' motor skills and body-control awareness with sport-specific maneuvers that consisted of balance, body control, plyometrics, and strengthening. Players worked in pairs and were instructed to give each other feedback during training. In total, 256 athletes (14 teams) performed the NMT and 201 athletes (14 teams) maintained their routine training. The subjects' mean age was 24.0 years old in both the intervention group and the control group.

Steffen et al, 2008 (PEDro Score 7, Level of Evidence 1b)

Using a cluster-randomized controlled design (2100 players, 113 teams), this research team prescribed 15 minutes of a structured warm-up program called "11." The 11, which consisted of core stability, balance, plyometrics, and hamstrings-strengthening exercises, was applied to 1073 young female soccer players (58 teams) for the first 15 consecutive sessions and once a week for the remaining 7½ months. Players and coaches were instructed to provide feedback for their movements during the exercises. The subjects' mean age was 15.4 years old for both the intervention group and the control group.

Gilchrist et al, 2008 (PEDro Score 4, Level of Evidence 1b)

In this randomized cluster-controlled study, investigators applied the 20-minute PEP program (previously developed by Mandelbaum et al) to high-level college female soccer teams.[37] The intervention and control groups were paired and formed a cluster. The clustered pairs were purposefully allocated in different geographic regions throughout the United States. Then, 1 cluster of each region was randomly selected for the study. Soccer players (583 players, 26 teams) categorized in the intervention group performed the PEP program 3 times per week for the entire fall soccer season (12 wk), and each PEP session was supervised by athletic trainers The reported subjects' mean age was 19.9 years for both the intervention and control groups.

Study name	Odds ratio	Lower limit	Upper limit	*P* value
Hewett et al 1999	0.503	0.097	2.609	0.414
Soderman et al 2000	5.310	0.578	48.779	0.140
Heidt et al 2000	0.762	0.093	6.255	0.800
Myklebust et al 2003	0.870	0.499	1.516	0.624
Mandelbaum et al 2005	0.179	0.077	0.413	0.001
Olsen et al 2005	0.318	0.086	1.181	0.087
Petersen et al 2005	0.206	0.024	1.787	0.152
Pfeiffer et al 2006	1.497	0.301	7.440	0.622
Steffen et al 2008	0.705	0.189	2.633	0.603
Gilchrist et al 2008	0.563	0.234	1.357	0.201
Pasanen et al 2008	1.182	0.329	4.246	0.798
Kiani et al 2010	0.085	0.005	1.535	0.095
LaBella et al 2011	0.340	0.068	1.688	0.187
Walden et al 2012	0.419	0.169	1.040	0.061
	0.541	0.354	0.828	0.005

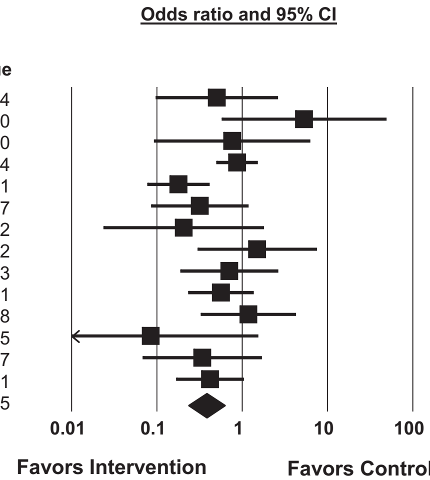

Figure 2. Anterior cruciate ligament injury risk reduction (meta-analysis with random model).

Kiani et al, 2010 (PEDro Score 4, Level of Evidence 2b)

This prospective cluster-controlled study (1506 players, 97 teams) included a 40-minute-long neuromuscular regimen consisting of a running warm-up, isometric contraction of the lower-extremity muscle groups, balance exercises with jump components, strengthening of the lower extremities, and core stability. In total, 777 young soccer players (48 teams) performed this training regimen 2 days per week for the 2-month preseason and once a week during the 6-month season. To ensure quality of the exercise instruction and performance, trained instructors visited teams upon their request. In this study, the subjects' mean age was 14.7 years for the intervention group and 15.0 years for the control group.

LaBella et al, 2011 (PEDro Score 6, Level of Evidence 1b)

Using a randomized cluster-controlled design, investigators applied a program called "Knee Injury Prevention Program" (KIPP), which is composed of 20 minutes of progressive strengthening, plyometrics, and balance and agility exercises to urban public high school soccer and basketball teams 3 times per week for 1 competitive season. Trained coaches instructed exercise performance and supervised each KIPP session. The subjects were of diverse socioeconomic, racial, and ethnic backgrounds, as well as competition levels, and the investigators stratified teams based on the socioeconomic and competition levels and randomly allocated the subjects in the intervention. In total, 53 teams received the intervention, which consisted of a total of 737 athletes: 321 soccer (43.6%) and 416 basketball (56.4%) players. The subjects' mean age was 16.2 years for both the intervention and control groups in this study.

Walden et al, 2012 (PEDro Score 7, Level of Evidence 1b)

This research team applied a cluster-randomized control design to a total of 4564 young soccer players (230 teams) and intervened with a 15-minute neuromuscular warm-up focused on the development of core stability, balance, and jump landing with proper knee alignment. Study therapists provided specific instruction of implemented exercises to 1 coach and a player from each team before the initiation of intervention. Coaches were responsible primarily for instruction of exercises, whereas a therapist made 2 unannounced visits to assist in the correction of training errors. A total of 2479 young soccer players (121 teams) trained 2 times per week for the entire competitive season (7 mo). The subjects' mean age was 14.0 years for the intervention group and 14.1 years for the control group in this study.

RESULTS

ACL Injury Risk Reduction (Overall)

A meta-analysis of the 14 included studies demonstrated significantly greater knee injury reduction in female athletes in the preventive NMT group compared with those who were in control group (OR: 0.54; 95% CI: 0.35, 0.83) (Figure 2).

ACL Injury Risk Reduction by Age of Subjects ($\leq$18 Versus >18 Years)

An age-dichotomized ($\leq$18 vs $>$18 y) meta-analysis was performed using the same 14 reviewed investigations. The results showed statistically greater knee injury risk reduction in female athletes who are $\leq$18 years of age

Age	Odds ratio	Lower limit	Upper limit	*P* value
> 18 years old	0.840	0.559	1.260	0.399
≤ 18 years old	0.278	0.184	0.420	0.001

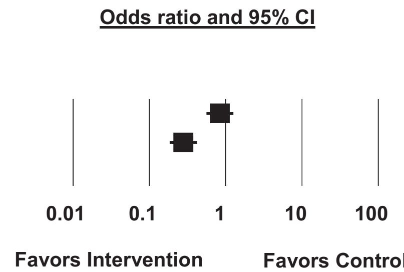

Figure 3. Anterior cruciate ligament injury risk reduction by age of subjects (≤18 years vs >18 years).

Age	Odds ratio	Lower limit	Upper limit	*P* value
Early Adults	1.011	0.622	1.643	0.966
Late Teens	0.476	0.212	1.071	0.073
Mid Teens	0.278	0.184	0.420	0.001

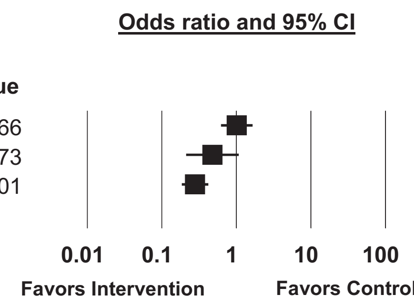

Figure 4. Anterior cruciate ligament injury risk reduction by tertile age categorization of subjects (mid-teens vs late teens vs early adults).

(OR: 0.28, 95% CI: 0.18, 0.42) compared with those who are >18 years old (OR: 0.84; 95% CI: 0.56, 1.26) (Figure 3).

ACL Injury Risk Reduction by Categorization of Subjects

An age tertile (mid-teens vs late teens vs early adults) meta-analysis was further applied to investigate the effect of age on knee injury risk. The result indicated statistically greater knee injury risk reduction in female athletes who were categorized as being in their mid-teens (14-18 y; OR, 0.28; 95% CI, 0.18-0.42) compared with female athletes who were categorized as being in their late teens (18-20 y) (OR, 0.48; 95% CI, 0.21-1.07) and early adults (over 20 years old; OR, 1.01; 95% CI, 0.62-1.64) (Figure 4).

Evidence Synthesis

The CEBM level of evidence of each clinical trial is listed in Table 1.[69] The CEBM level of evidence can further generate a grade of strength of recommendation based on the level of consistent evidence, which is composed of A through D. In the current analysis, 7 of the included were rated as level 1b (randomized control trial),[§§] whereas 7 investigations were rated as level 2b (cohort study including low quality randomized control trial).[‖‖] Based on consistency of the results from the included investigations, the strength of recommendation grade for the current evidence is A (consistent level 1 investigations).

Bias Assessment

The Egger regression interception plot was used to assess potential publication bias. The interception plot of the 14 reviewed studies (–0.17; 95% CI, –1.93 to 1.59; P =.42, 1-tailed) indicated that publication bias was not found with the current analysis.

DISCUSSION

The current meta-analysis revealed an age-related association between NMT implementation and reduction of ACL injury incidence, and therefore, the tested hypothesis that NMT would show greater efficacy in younger populations was accepted. The dichotomized analysis for ACL injury based on age under and over 18 years demonstrated 72% risk reduction in female athletes under 18 years old; however, for female athletes over 18 years old, the rate was only 16% (Figure 3). These results indicate that it may be optimal to implement NMT programs during pre- or early adolescence, before the period of altered mechanics that increase injury risk. In fact, the current data indicate that pre- or early adolescents (mid-teens) showed the greatest risk reduction (72%) compared with late

[§§]References 21, 22, 34, 58, 60, 67, 70.
[‖‖]References 25, 33, 37, 55, 61, 62, 66.

adolescents (late teens; 52% of risk reduction) (Figure 4). Unexpectedly, the current analysis did not demonstrate ACL injury risk reduction in early adults compared with early and late adolescents (Figure 4). This finding may be interpreted that ACL injury odds were 1.7 times higher in late teens compared with pre- or early adolescents (mid-teens) (Figure 4). Similarly, ACL injury odds in early adults was noted to be 3.6 times higher in relation to pre- or early adolescents (mid-teens) after NMT (Figure 4). It indicates that the prophylactic effectiveness of NMT is more pronounced in pre- or early adolescent–aged athletes. The current data could indicate that the potential window of opportunity for optimized ACL injury risk reduction may be before the onset of neuromuscular deficits and peak knee injury incidence that occurs after the onset of maturation in female athletes and/or during the mid-teen years.

Previous reports have suggested that the interventions that include pre- or early adolescents (early teens) may be more effective in reducing ACL injury risk compared with interventions implemented in late adolescents and early adult–aged female athletes.[44,45] The results of the current investigation support the contention that younger athletes may be more receptive to NMT, which will lower their risk of injury (Figure 4). This higher risk of injury in postpubertal athletes has been attributed to several changes that occur throughout the pubertal period, such as structural/anatomic changes, hormonal variations, and decreased strength. This particular age group spans the typical pubertal development stages (prepubertal, pubertal, and postpubertal), which is not true of the other age groups within this review, and may provide some insight into the reason this age difference was demonstrated. Pubertal status has been associated with risk of injury in that postpubertal athletes are at higher risk of injury. Although this increased risk is not seen in prepubertal or pubertal athletes, the findings of this review indicate that training athletes during these pubertal stages may be most effective for prevention of ACL injuries.

Another potential explanation for the greater NMT effectiveness in the pre- or early adolescent age group may be variability. Although speculative, it may be that a large variability exists in the "quality" of athletes participating in cutting, pivoting, and jumping sports such as soccer, volleyball, and basketball in the younger ages. As they become older, the lower level athletes have ceased participation as a result of skill level, athletic ability, and different interests. Investigators have suggested that targeting NMT to athletes who are at high risk results in a greater reduction of injury risk.[46] Although it is beyond the scope of the current investigation, future studies that evaluate the effectiveness of knee injury prevention programs between different sports and levels of participation within those sports are warranted.[44,45]

Pathomechanics/Mechanisms of Knee Injury in Adolescents: Are They Different Than Adults?

Schmikli et al[64] investigated the differences in injuries between junior (4-17 y) and senior (18-35 y) male soccer programs in the Netherlands. The incidence of injury was found to be almost twice as high in the senior group as compared with the junior group, even though exposure time was comparable between the groups. Within the senior group, the largest incidence of injury was found among the athletes who were in the 3 to 5 and 5+ hours per week exposure groups.[64] In an injury surveillance project involving 12- to 19-year-old Portuguese soccer players,[6] male athletes were tracked through the preseason training and competition. Although no difference in injury incidence across age ranges was noted, there was a significant finding in that incidence was higher during matches in the older groups (U19 and U17) when compared with incidence of injury during training. This difference was not present in the younger age groups, possibly indicating that there is a larger difference between intensity of practice and match play in the older groups when compared with the younger groups. Interestingly, interventions focused to reduced knee injury appear to be effective when implemented in boys and girls.[63]

Training Programs for Youth

Although many investigations have examined the efficacy of injury prevention training programs for adolescent and adult athletes, the authors of a recent study designed and implemented an intervention specifically for the pediatric athlete (mean age, 10 ± 1 y).[9] This pediatric program implemented more progressive exercises in comparison with the traditional intervention but included the same principles of balance, strengthening, flexibility, and agility exercises. Results indicated that subjects in the pediatric training group demonstrated a lower peak internal knee rotation at initial contact of a cutting maneuver after completion of the training program. The traditional training program did not elicit any measured changes, indicating that injury-prevention protocols should be tailored to meet the needs of a pediatric population in order to elicit changes in movement patterns.

A recent meta-analysis of youth resistance training indicated that improved muscular strength is dependent on adequate volume to provide sufficient adaptive stimulus, and resistance training is an effective method for motor performance in children and adolescents.[3] The traditionally effective training programs previously used in adolescents were modified into a 9-week "integrated injury prevention program" for use as an additive training regimen during the warm-up period in young soccer players (10-12 y).[10] The addition of the integrative injury prevention training program into standard soccer training influenced improvements in balance ability and vertical jump height in the young soccer players.[10] The data from the current investigation clearly indicate that participation in physical activity should not begin with competitive sport, but rather, it should evolve out of well-rounded preparatory fitness conditioning that is sensibly progressed over time. With the addition of integrative NMT into physical education classes, after-school activities, and sport practice sessions, teachers and coaches can be better equipped to ensure that youth will see greater gains in both health- and skill-related physical fitness with likely reductions in the risk of sports-related injury.[43] One study implemented a 10- to 15-minute preventive NMT program 3 or 4 times per week and evaluated motor learning retention ability of the lower extremities.[11] Another study assessed jump-landing movement patterns based on 3-month and 9-month groups and reported that the 9-month group retained the learned landing movement patterns in 3 months post-ACL prevention training program, whereas the landing movement patterns of the subjects in the 3-month group return to prestudy levels after 3 months without training.[59]

Faigenbaum and colleagues[11] evaluated an integrative NMT program that was performed twice per week during the first approximately 15 minutes of 7-year-old students' (second grade) physical education class. This integrative NMT program consisted of body weight exercises that focused on the enhancement of muscular strength, muscular power, and fundamental movement skills. These data indicated that integrative NMT is an effective and time-efficient addition to physical education, as demonstrated by improvements in health- and skill-related fitness measures in children. High compliance and self-reported positive attitudes toward integrative NMT provided evidence of the feasibility and value of incorporating integrative NMT into pediatric and youth fitness programs.[11] The authors indicated that incorporation of integrative NMT programs at an age as early as 7 years old is a cost-effective and time-efficient method for enhancing motor skills, promoting physical activity in children, and reducing their future injury risk during adolescence. Interestingly, the 7-year-old *girls* who had integrative NMT included with their standard physical education appeared to be particularly sensitive to the effects of integrative NMT, suggesting a potential sex-specific window for optimum implementation.[14] Preliminary data indicate integrative NMT protocols implemented in preadolescence (Tanner 1) and early adolescence (Tanner 2) may artificially induce the "neuromuscular spurt" (defined as the natural adaptation of increased power, strength, and coordination that occurs with increasing chronological age and maturational stage in adolescent boys), especially related to relative posterior chain strength postural control and neuromuscular power, which is often reduced as young female athletes mature.[41,45] Cumulatively, these recent data provide further support that preadolescence may be an optimal time to institute programs aiming to reduce these deficits that accelerate during maturation and lead to increased musculoskeletal injury risk.

Key Training Components to Prevent Injury in Youth. The training modalities employed in the design of NMT to prevent serious knee and ACL injury have been varied, using many different types of NMT. A prior systematic review of the literature reported that several different training protocols have incorporated multiple components targeted toward injury-prevention training.[23,29] The prior reports on training to prevent injury across all age groups indicates that plyometric training combined with biomechanical analysis and technique-driven feedback were common components in the interventions that effectively reduced ACL injury rates.[23] Conversely, an investigation that employed only a series of isolated plyometric exercises as an intervention without feedback-driven instruction did not report a reduction of injury with a documented equal number of noncontact ACL injury between NMT and control groups.[62] Similarly, in analyses that incorporate all age categories, balance training alone did not appear to provide the needed stimulus to reduce ACL injury risk.[23] In fact, isolated balance training without feedback-driven instruction appeared to be the least effective approach in the current meta-analysis (Figure 2).[66]

The current meta-analysis also indicates that in young athletes, balance training may be most effective for injury prevention when it is combined with other types of training. Although Kiani and colleagues[33] employed dynamic stabilization between jumping tasks in their training with the younger age category, it appears that balance- and strength-focused exercises combined with biomechanical feedback appear to be key elements for injury prevention in young athletes. In addition, compliance with the NMT needs to be considered as an important aspect. A recent study that analyzed the effects of compliance on NMT found an inverse association between NMT compliance and ACL injury rates.[68] Reduced compliance was also indicated by the authors as it related to their program's relative ineffectiveness in reducing noncontact lower-extremity injuries.[60] In-season training may be effective to improve the needed compliance and dosage with exercise training protocols,[68] but unfortunately, isolated, in-season-only training may not benefit young athletes in the first half of the competitive season without the opportunity to gain the beneficial injury-prevention effects in the early season.[21] Also, the inability to implement robust progression protocols of varying intensity with in-season-only programs likely precludes measurable performance-enhancement effects.[52] The current data indicate that the most effective and efficient youth injury-prevention programs appear to require a combination of components including plyometrics, dynamic stabilization, strength, and feedback-driven technique training, and the effects of these components are potentially additive when employed during both the preseason and season.

Instruction and Supervision for Successful Implementation of NMT in Youth. Most importantly, it is likely that proper supervision and feedback on exercises was a common thread throughout the effective NMT protocols. Qualified instruction is integral to ensure that young athletes are performing exercises properly and not reinforcing bad movement mechanics, which puts them at risk for injury.[40,46,49] In the current investigation, the 2 reviewed studies that provided isolated training modalities with limited or no feedback-driven instruction also showed no injury-reduction effects of NMT.[62,66] Age-appropriate education and qualified instruction enhance successful integration of critical components (plyometrics, balance and dynamic stabilization, strength and biomechanical feedback) related to the mastery of fundamental movements.[50] Although there is no minimum age for participation in properly structured and supervised injury-prevention training programs, all participants must be able to follow coaching instructions and be able to handle the attention demands required to receive feedback and instruction during exercise implementation.[45] The prescribed exercises, sets, and repetitions for an effective integrative neuromuscular exercise program should be feasible for each athlete and modified as needed. Initial volume selection should be low to support development of proper technique with exercises.[44] Volume (or resistance, when applicable) should be increased after the athlete can properly perform the exercise at the prescribed volume and intensity. The professionals who supervise young athletes should be skilled in recognizing proper technique and be able to provide constructive feedback during the learning process, especially during exercises during which improper technique increases injury risk.[11-13,50] As indicated by the results of the current study, the benefits of proper exercise instruction and feedback cannot be overlooked in effective NMT programming for youth.

Long-term Effects of Knee Injury in Young Athletes and the Importance of Injury Prevention

Acute injuries early in life can have longstanding effects on those athletes who suffer injuries in their adolescent period. One study reported that 14% of men who suffered a knee injury during adolescence presented with radiographic evidence of OA by the age of 65 years, as compared with only 6% in those who did not suffer a knee injury during the young adult stage of life.[20] The long-term effects of an ACL injury are evident in the incidence rates of OA in the injured knee, which occurs in 41% to 51% of injured knees as opposed to 4% to 8% in the uninjured legs of soccer players.[7] Meniscus injury and subsequent surgery also have long-term effects on knee joint health. Several investigations that completed follow-up reports of those with meniscus surgery indicated that approximately 50% suffer with knee OA and joint pain and dysfunction.[7] Regardless of the treatment strategy (nonoperative management versus operative treatment), OA occurs at 10 times the normal rate in ACL-injured individuals, and there may be a nearly 100% chance of OA after ACL injury after 20 years.[15,54] In addition, another study reported that patients with OA after the ACL injury hinder knee-related quality of life.[36] These data provide strong evidence of the need to prevent knee injury, especially in our youth.

CONCLUSION

Sports-related ACL injuries increase during adolescence and peak in incidence during the mid- to late teens in female athletes. In response to these high rates of injury, NMT programs are often prescribed to reduce the ACL injury incidence in these populations. Longitudinal biomechanical investigations indicate that a potential window of opportunity is present before the peak injury incidence, which would be optimal timing for the initiation of integrative NMT in female athletes. However, the influence of the timing of initiation of these programs on the efficacy of ACL injury reduction has yet to be evaluated. Therefore, our objective was to systematically review and synthesize the scientific literature in regard to the influence of age at NMT implementation on the effectiveness for reduction of knee and ACL injury incidence. The current meta-analysis demonstrated prophylactic effects of NMT to prevent ACL injury in female athletes. In addition, the analysis based on age categorizations demonstrated more pronounced prophylactic effects of NMT if the NMT is performed at younger ages. The hypothesis was supported that injury-prevention training focused to reduce knee and specific ACL injury would be most effective in the youngest populations. Further research in children and adolescents is warranted to further investigate the potential to prevent injury with interventions targeted at younger athletes.

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