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SYSTEMATIC REVIEW

Dosage Effects of Neuromuscular Training Intervention to Reduce Anterior Cruciate Ligament Injuries in Female Athletes: Meta- and Sub-Group Analyses

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Abstract
Background Although a series of meta-analyses demonstrated neuromuscular training (NMT) is an effective intervention to reduce anterior cruciate ligament (ACL) injury in female athletes, the potential existence of a dosage effect remains unknown.
Objective Our objective was to systematically review previously published clinical trials and evaluate potential dosage effects of NMT for ACL injury reduction in female athletes.
Design This study took the form of a meta- and subgroup analysis.
Setting The keywords 'knee', 'anterior cruciate ligament', 'ACL', 'prospective', 'neuromuscular', 'training', 'female', and 'prevention' were utilized in PubMed and EBSCO host for studies published between 1995 and May 2012.
Participants Inclusion criteria set for studies in the current analysis were (i) recruited female athletes as subjects, (ii) documented the number of ACL injuries, (iii) employed an NMT intervention aimed to reduce ACL injuries, (iv) had a control group, (v) used a prospective control trial design, and (vi) provided NMT session duration and frequency information.
Main outcome measures The number of ACL injuries and female athletes in each group (control and intervention) were compared based on duration, frequency, and volume of NMT via odds ratios (ORs).
Results A total of 14 studies were reviewed. Analyses that compared the number of ACL injuries with short versus long NMT duration showed greater ACL injury reduction in female athletes who were in the long NMT

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duration group (OR 0.35, 95 % CI 0.23–0.53, $p = 0.001$) than in those in the short NMT duration group (OR 0.61, 95 % CI 0.41–0.90, $p = 0.013$). Analyses that compared single versus multi NMT frequency indicated greater ACL injury reduction in multi NMT frequency (OR 0.35, 95 % CI 0.23–0.53, $p = 0.001$) compared with single NMT frequency (OR 0.62, 95 % CI 0.41–0.94, $p = 0.024$). Combining the duration and frequency of NMT programs, an inverse dose-response association emerged among low (OR 0.66, 95 % CI 0.43–0.99, $p = 0.045$), moderate (OR 0.46, 95 % CI 0.21–1.03, $p = 0.059$), and high (OR 0.32, 95 % CI 0.19–0.52, $p = 0.001$) NMT volume categories.

Conclusions The inverse dose-response association observed in the subgroup analysis suggests that the higher the NMT volume, the greater the prophylactic effectiveness of the NMT program and increased benefit in ACL injury reduction among female athletes.

1 Introduction

Since the inception of Title IX of The Educational Assistance Act in 1972, the number of female athletes at high school level has increased more than elevenfold (from 0.3 to 3.2 million), whereas the increase in male athletes has been approximately 1.2-fold (from 3.7 to 4.5 million) in the USA [1]. Along with the increase in number of female athletic participants, the number of resultant athletic injuries among female athletes has also increased rapidly. Among many types of debilitating injuries, female athletes have shown susceptibility to knee joint injury, especially anterior cruciate ligament (ACL) injury. In high school basketball, it has been reported that one in every 81 female athletes experienced an ACL injury [2, 3] and that the total number of ACL injuries among female athletes was estimated to be approximately 38,000 annually in the USA as of 2001 [4]. A similar trend has also been reported at the college level, as data from the National Collegiate Athletic Association (NCAA) from 1989 to 1998 demonstrated female soccer and basketball players have 2.4 times and 4.1 times higher risk for an ACL injury than their male counterparts in the same sports at college level, respectively [5].

The disproportionately higher ACL injury risk in female athletes compared with their male counterparts is considered multi-factorial in nature and is often discussed from anatomical, hormonal, and biomechanical standpoints [6, 7]. Several biomechanical studies found elevated knee abduction, limited knee flexion, asymmetrical landing patterns, higher ground reaction force, and poor trunk control are predictors for future ACL injuries in young female athletes [8–10]. Consequently, a few intervention studies have examined the effectiveness of neuromuscular training (NMT) through alteration of the biomechanical ACL risk factors, and a majority of the studies demonstrated prophylactically favorable alteration [11–14]. However, findings from the laboratory do not seem to have translated as well to clinical environments. In fact, the ACL injury rate continues to rise annually [15]. One of the reasons may be related to inconsistent findings within the previous ACL prevention clinical trials. A few clinical trials that used NMT as an intervention demonstrated a significant ACL injury reduction [16–18]. Conversely, several NMT clinical trials did not show ACL injury reduction [19, 20]. For instance, using a specialized NMT called 'prevent injury and enhance performance', one study demonstrated an 88 % ACL injury reduction in the intervention group [18]; conversely, another actually recorded a greater number of ACL injuries in the intervention group compared with the control group [19]. To determine the evidence as to whether or not NMT is an effective intervention for ACL injury reduction in female athletes, a meta-analysis was conducted and demonstrated effectiveness of NMT as an intervention on ACL injury reduction in female athletes [21] (Fig. 1).

Although the most recent meta-analysis report [21] and other studies [22, 23] identified NMT programs as useful interventions to reduce ACL injuries in the female population, there is no clear answer for the heterogeneity of the ACL injury reduction differences within the clinical trials [16–20]. One potential reason to explain the disparity in injury reduction rates may be related to the dosage of the NMT programs. An unrelated study evaluated the effectiveness of neck rehabilitation and demonstrated that the rehabilitation exercises were effective when performed three times per week, but not when performed two times per week [24]. Additionally, one of the recent clinical trials that utilized NMT as an intervention for female athletes to reduce ACL injury concluded that the NMT effect is "likely dose related" [25]. Several clinical trials that aimed to reduce ACL injuries stated that too few NMT sessions is a limitation and may be a reason that desirable treatment effects were not obtained [26, 27]. Since a previous meta-analysis has confirmed the effectiveness of an NMT intervention to reduce ACL injury in young female athletes (Fig. 1), the current project was designed to examine dosage effects of NMT, which were analyzed based on duration and frequency of NMT sessions. Therefore, the purpose of the current analysis was to systematically review previously published NMT intervention clinical trials that aimed to reduce ACL injury in female athletes and evaluate whether or not a higher NMT dosage enhanced the prophylactic effectiveness of NMT on ACL injury in young female athletes.

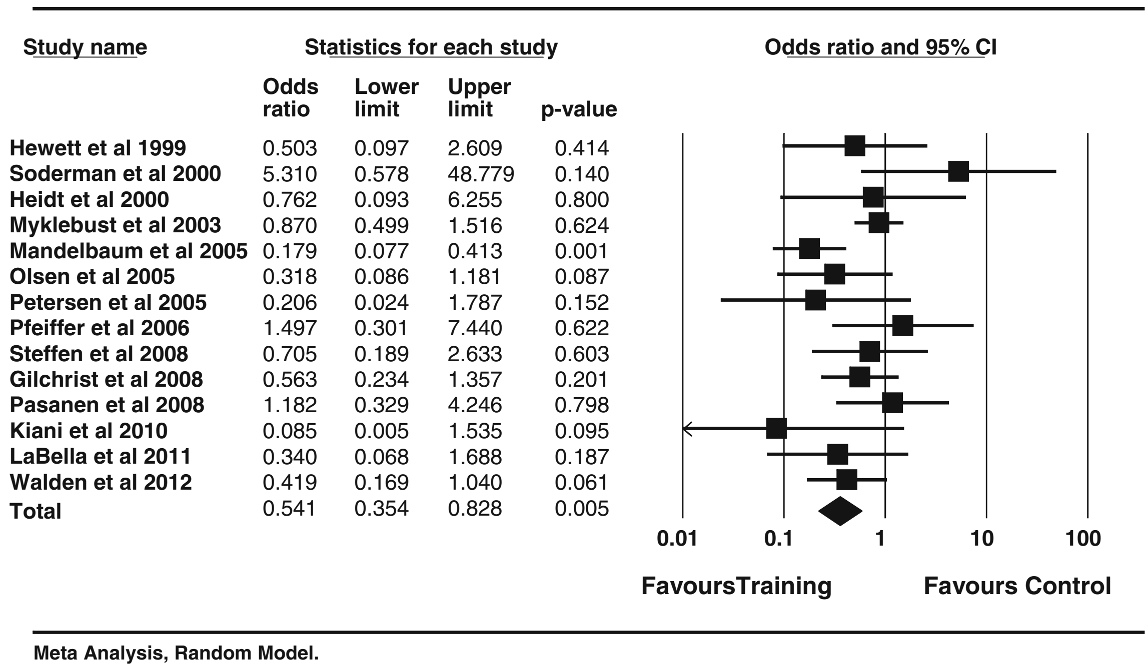


Fig. 1 A meta-analysis of 14 clinical trials—anterior cruciate ligament injury (adapted from Myer et al. [21] with permission)

2 Methods

2.1 Literature Search and Criteria

A literature search was performed on 31 May 2012 using the PubMed and EBSCO host (CINAHL, MEDLINE, and SPORTDiscus) from 1995 to 2012. The keywords searched were performed by applying a combination of the following words: 'knee', 'anterior cruciate ligament', 'ACL', 'prospective', 'neuromuscular', 'training', 'female', and 'prevention' (Table 1). Language was limited to English, and subjects were all human. The following criteria were examined by the two independent reviewers to meet inclusion: (i) the number of ACL injury incidents were reported, (ii) an NMT intervention that aimed to reduce ACL incidence was applied, (iii) a control group was used, (iv) a prospective controlled trial study design was employed, (v) females were included as subjects, and (vi) NMT duration and frequency information were provided. Abstracts, posters, and unpublished data were not included in the final analysis. During this process, discrepancies in inclusion and exclusion of studies such as holding very similar characteristics of the above inclusion criteria were discussed among the primary author (DS) and the second author (GDM). Egger's regression was used to examine a potential risk of publication bias.

2.2 Quality of Methodology Evaluation Method

The Physiotherapy Evidence Database (PEDro) scale was used to analyze methodological quality of the included

Table 1 Stepped PubMed/EBSCOhost search strategy with the number of studies

Step	Strategy	PubMed	EBSCO
#17	Search (#11) AND (#16)	402	76
#16	Search (#12) OR (#13) OR (#14) OR (#15)	24897	41136
#15	Search "preventing" [TIAB]	5101	1122
#14	Search "preventive" [TIAB]	2496	2348
#13	Search "prevent" [TIAB]	8551	2003
#12	Search "prevention" [TIAB]	13521	14814
#11	Search(#5) AND (#10)	4377	3616
#10	Search (#6) OR (#7) OR (#8) OR (#9)	76185	75651
#9	Search "female" [TIAB]	15605	25488
#8	Search "training" [TIAB]	10336	26450
#7	Search "neuromuscular" [TIAB]	1455	2646
#6	Search "prospective" [TIAB]	52817	21939
#5	Search (#1) OR (#2) OR (#3) OR (#4)	13050	60968
#4	Search "ACL" [TIAB]	438	1104
#3	Search "anterior cruciate ligament" [TIAB]	565	4330
#2	Search "knee" [TIAB]	5074	18321
#1	Search "injury" [TIAB]	8156	39322

Date were limited to publication from 1 January 1995 to 31 May 2012. Language was limited to English. Species were limited to humans. Sex was limited to female. MEDLINE was used for a journal category selection for PubMEd. CINAHL, MEDLINE, and SPORT-Discus were included in the EBSCO search

TIAB title and abstract

studies. The PEDro scale is a widely utilized measurement tool to rate the methodological quality of the randomized clinical intervention trials. The PEDro scale of the study reviewed was reported in the previous study [21].

2.3 Level of Evidence and Strength of Recommendation Assessment Method

To evaluate the quality of the current analysis, the Strength of Recommendation Taxonomy (SORT) was implemented [28]. The SORT is used to evaluate the quality of the included studies and the strength of recommendation, which facilitates the generation of a grade of strength of recommendation for the current analyses.

2.4 Data Extraction

The number of ACL injuries in each group (control and intervention) and the number of subjects in each group (control and intervention) were extracted for data analysis by the primary author. The number of ACL injuries was carefully reviewed and extracted. To examine the dosage effect, the time used for each NMT session (NMT session) and the number of NMT sessions per week (NMT frequency) were also reviewed and extracted from each study. Where the necessary information for the analysis was not documented in the published manuscript, an email was sent to the corresponding author listed in the original paper and a request for NMT duration and frequency information was made.

2.5 Operational Definitions

To examine the dosage effects, reviewed trials were dichotomized based on the status of the extracted NMT duration and NMT frequency. For the NMT duration, short and long periods were defined as follows:

1. Short NMT duration = less than 20 min of NMT per session
2. Long NMT duration = more than 20 min of NMT per session.

Likewise, the NMT frequency was defined as either single or multi using the following definitions:

3. Single NMT frequency = one session of NMT per week during in-season
4. Multi NMT frequency = at least two sessions of NMT per week during in-season.

Finally, the session length and session frequency were combined and defined as NMT volume. The following definitions were used for low, moderate, and high NMT volume:

5. Low NMT volume = up to 15 min per week was spent for NMT during in-season
6. Moderate NMT volume = 15–30 min per week was spent for NMT during in-season
7. High NMT volume = more than 30 min per week was spent for NMT during in-season.

2.6 Data Analysis

To evaluate NMT effectiveness and the potential dosage effects, a series of subgroup analyses with 95 % confidence intervals (CIs) were employed. The NMT duration was examined based on short versus long NMT duration. Likewise, single versus multi NMT frequency was analyzed for assessing potential dosage effects of NMT frequency. Lastly, NMT volume was compared with low, moderate, and high NMT volume.

To compare a ratio of ACL injuries in subjects between intervention and control groups, an odds ratio (OR) was used. Because we assumed that the effect size of each study was different, a random-effects model was chosen to minimize variability among the included studies. I^2 statistics were calculated to express total variation across studies due to heterogeneity as opposed to random chance. The significance level of the heterogeneity was set at 0.05 a priori. Egger's regression and trim and fill plot were used to examine potential risks of publication bias assessment. I^2 statistics were employed to check heterogeneity of the sub-group analyses. The alpha level of the I^2 was set at <0.05 a priori. All analyses were performed by comprehensive meta-analysis software (Biostat, Englewood, NJ, USA).

3 Results

A total of 459 original studies were collected, including cross-referenced studies resulting in 13 clinical trials that met the inclusion criteria of the current analyses. One study [26] that did not completely fulfill the inclusion criteria because of an absence of control group due to the study design (cross-over design) was actually included since the study fulfilled the rest of the inclusion criteria and met the purpose of the current project. Thus, a total of 14 studies [16–20, 25–27, 29–34] were included in the current analyses (Fig. 2). The quality of each study, number of ACL injuries, length and frequency of each NMT program, and other related information are summarized in Table 2. The relevant methodological quality as evaluated by the PEDro scores was reported in the previously published study [21].

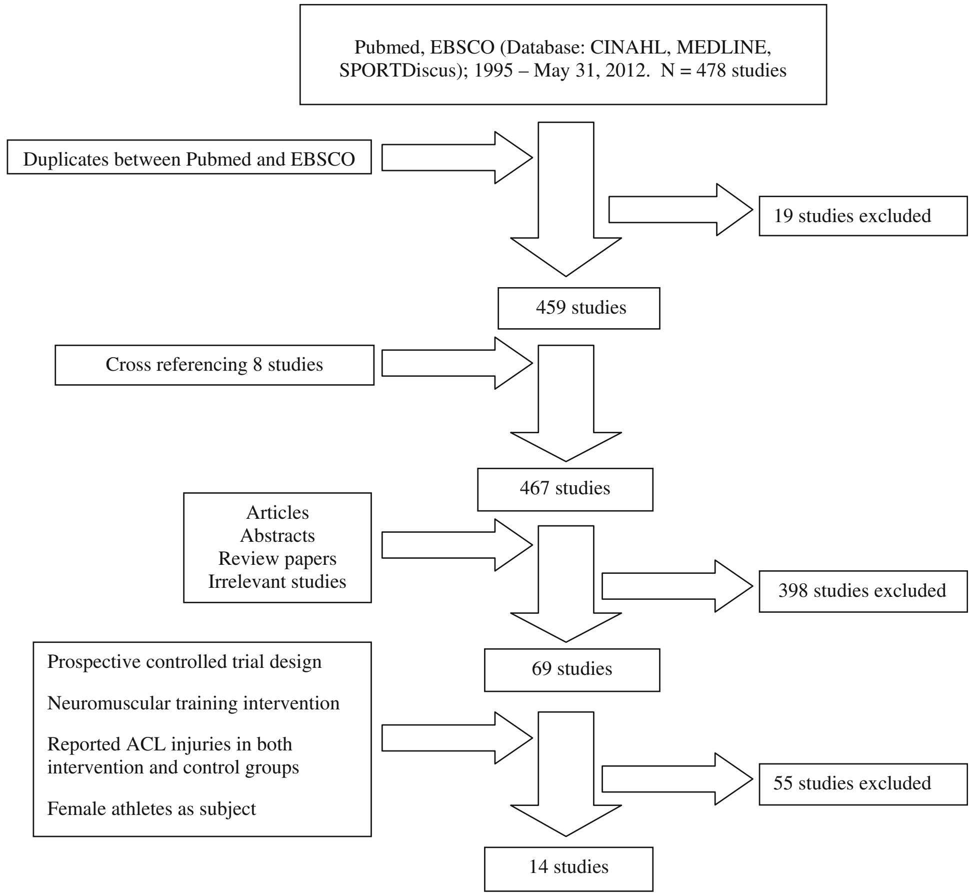


Fig. 2 A flow chart of literature review. *ACL* anterior cruciate ligament

3.1 Anterior Cruciate Ligament (ACL) Injury: Neuromuscular Training (NMT) Duration of 14 Clinical Trials

The sub-group analysis that compared the number of ACL injuries with short versus long NMT duration within the 14 reviewed clinical trials [16–20, 25–27, 29–34] indicated greater ACL injury reduction in the long NMT session (OR 0.35, 95 % CI 0.23–0.53, $p = 0.001$) than in the short NMT session (OR 0.61, 95 % CI 0.41–0.90, $p = 0.013$) (Fig. 3).

3.2 ACL Injury: NMT Frequency of 12 Clinical Trials

Two clinical trials [16, 29] were removed from this analysis since they were pre-season programs and the remainder of the clinical trials had in-season NMT components; thus, the two clinical trials [16, 29] were not comparable. Comparison of the number of ACL injuries with single versus multi NMT frequency with 12 reviewed clinical trials [17–20, 25–27, 30–34] demonstrated greater ACL injury reduction in the multi NMT frequency groups (OR 0.35, 95 % CI 0.23–0.53, $p = 0.001$) than in the single (OR 0.62, 95 % CI 0.41–0.94, $p = 0.024$) (Fig. 4).

3.3 ACL Injury: NMT Volume of 12 Clinical Trials

The aforementioned two clinical trials [16, 29] were removed from this analysis because they were implemented as pre-season NMT programs and the remainder of the clinical trials were in-season NMT programs; thus, the two clinical trials [16, 29] did not match with three categories for this analysis. The number of ACL injuries was evaluated based on low versus moderate versus high NMT volume classification with a total of 12 clinical trials [17–20, 25–27, 30–34]. The analysis showed the greatest ACL injury reduction in the high NMT volume (OR 0.32, 95 % CI 0.19–0.52, $p = 0.001$), followed by the moderate (OR 0.46, 95 % CI 0.21–1.03, $p = 0.059$) and the low (OR 0.66, 95 % CI 0.43–0.99, $p = 0.045$) NMT volume programs (Fig. 5).

3.4 Evidence Synthesis

The SORT level of evidence of each clinical trial is shown in Table 2. The SORT level of evidence can further generate a grade of strength of recommendation (from A to C) based on the level of consistent evidence. In the current analysis, seven of the included clinical trials [25, 27, 29,

Table 2 Summary of studies included in the review

References	Study design	Level of evidence	Sports	Number of teams	Age, years (mean ± SD)[a]	Type	Length (min)	Frequency	Weekly time spent during in-season
Hewett et al. [16]	pro, non-ran cohort	II	Soccer, volleyball, basketball	15 (C) 15 (I)	14–18 (range)	Stretching, plyometrics, weight training	60–90	3 days/week pre-season	N/A[b]
Soderman et al. [19][c]	pro, ran control	II	Soccer	6 (C) 7 (I)	C:20.4 ± 5.4 I: 20.4 ± 4.6	Balance with balance boards	10–15	Each day for 30 days. 3 days/week rest of the season	10–15 min
Heidt et al. [29][d]	pro, ran control	I	Soccer	258 ind (C) 42 ind (I)	14–18 (range)	Cardiovascular, plyometrics, strength, flexibility, agility, and sport-specific drills	75	3 days/week pre-season	N/A[b]
Myklebust et al. [26]	pro, non-ran, cross-over	II	Handball	60 (1st year) 58 (2nd year) 52 (3rd year)	21–22	Balance with mats and wobble boards	15	3 days/week for 5–7 weeks. Once/week for rest of season	15 min
Mandelbaum et al. [18]	pro, non-ran cohort	II	Soccer	207 (C) 97 (I)	14–18 (range)	Basic warm-up, stretching, strengthening, plyometrics, agility	20	2–3 times/week in-season	40–60 min
Olsen et al. [30]	pro, cluster, ran controlled	I	Handball	59 (C) 61 (I)	16–17	Warm-up, technique, balance, strength, power	15–20	15 consecutive sessions. Once/week for rest of season	15–20 min
Petersen et al. [31][e]	pro matched cohort	II	Handball	10 (C) 10 (I)	C:19.8 I: 19.4	Education, balance-board exercise, jump training	10	3 times/week pre-season. Once/week for rest of season	10 min
Pfeiffer et al. [20]	pro, non-ran cohort	II	Soccer, volleyball, basketball	69 (C) 43 (I)	14–18 (range)	Plyometrics	20	2 times/week in-season	40 min
Steffen et al. [27]	pro, block, ran controlled	I	Soccer	51 (C) 58 (I)	15.4	Core stability, balance, plyometrics	15	15 consecutive sessions. Once/week for rest of season	15 min
Gilchrist et al. [32]	Pro cluster ran, controlled	I	Soccer	35 (C) 26 (I)	C:19.9 I: 19.9	Basic warm-up, stretching, strengthening, plyometrics, agility	20	3 times/week in-season	60 min
Pasanen et al. [33]	pro, cluster, ran, controlled	I	Floorball	14 (C) 14 (I)	24	Running techniques, balance, body control, plyometrics, strengthening	20–30	2–3 times/week pre-season (intensive training period), once/week in in-season (maintenance period)	40–90 min
Kiani et al. [17][f]	pro cluster, non-ran cohort	II	Soccer	49 (C) 48 (I)	C: 15.0 I: 14.7	Core strengthening, balance	20–25	2 days/week for 2 months. Once a week for rest of season	20–25 min

Table 2 continued

References	Study design	Level of evidence	Sports	Number of teams	Age, years (mean ± SD)[a]	Type	Length (min)	Frequency	Weekly time spent during in-season
LaBella et al. [25]	pro cluster, ran, controlled	I	Soccer, basketball	53 (C) 53 (I)	C: 16.2 I: 16.2 years	Strengthening, plyometrics, balance, agility	20	3 times/week pre- and in-season	60 min
Walden et al. [34]	pro, cluster, ran, controlled	I	Soccer	109 (C) 121 (I)	C: 14.1 I: 14.0	Core stability, balance, jump-landing with knee alignment feedback	15	2 times/week	30 min

C control group, *I* intervention group, *ind* individuals, *N/A* not applicable, *NMT* neuromuscular training, *pro* prospective, *ran* randomized

[a] Unless otherwise indicated

[b] The NMT was performed only during a pre-season

[c] Although the study was a randomized controlled design, the follow-up rate was low (51.2 %). Therefore, the level of evidence was rated as II

[d] For analysis purposes, only data from the first year intervention year were used

[e] Although there was no specific statement, the NMT indicated plyometric components

[f] Although there were jump-landing maneuvers, repeated stretch-shortening cycles were not employed in the training

30, 32–34] were rated as level I (high-quality individual randomized control trial), while seven clinical trials [16–20, 26, 31] were rated as level II (lower-quality clinical trial and cohort study). Although the number of level I and II clinical trials are equivalent, the current meta-analysis supports consistency of evidence, since 11 of the 14 reviewed clinical trials demonstrated fewer ACL injuries in the NMT intervention group compared with control groups. In addition, a summary effect of the meta-analysis (Fig. 1) supports the evidence consistency. Based on the consistency of the results from the included clinical trials, the strength of recommendation grade for the current evidence is A (recommendation based on consistent and good-quality patient-oriented evidence).

3.5 Heterogeneity

The I^2 statistics of the subgroup NMT analysis for duration, frequency, and volume indicated p values greater than 0.05 ($p = 0.06$ for duration, $p = 0.06$ for frequency, and $p = 0.09$ for volume). Since the p value did not reach statistical significance, the heterogeneity effects were considered minimal.

3.6 Bias Assessment

Egger's regression for the publication bias for the 14 reviewed clinical trials showed an interception -0.17 (95 % CI -1.93 to 1.59, $p = 0.41$, one tailed), indicating no publication bias in the current analysis, and the trim and fill plot also displayed no publication bias (Fig. 6).

4 Discussion

The previously performed meta-analysis generated an OR of 0.54 (95 % CI 0.35–0.83, $p = 0.05$; Fig. 1) ensuring effectiveness of NMT as an intervention demonstrating 46 % of risk reduction for suffering an ACL injury compared with those who did not perform NMT. Although the reviewed NMT clinical trials were fairly diverse (Table 2), closely examining NMT programs from a dosage standpoint, several key NMT elements appear to relate to greater ACL injury reduction: NMT duration, frequency, and volume. Relative to dosage effect, the two dichotomized sub-group analyses (short vs. long NMT duration and single vs. multi NMT frequency analyses) resulted in more significant prophylactic effects in the long NMT duration and multi NMT frequency groups compared with the short NMT duration and single NMT session groups. The two dichotomized sub-group analyses demonstrated dosage effects between duration and frequency of NMT programs and number of ACL injuries in young female athletes. It

Variable	Odds ratio	Lower limit	Upper limit	p-Value
Short NMT session	0.610	0.412	0.902	0.013
Long NMT session	0.350	0.230	0.533	0.001

Statistics for each variable; Odds ratio and 95% CI

Sub-group Analysis, Random Model

Fig. 3 Subgroup analysis of NMT duration and anterior cruciate ligament injury in 14 clinical trials. *NMT* neuromuscular training

Variable	Odds ratio	Lower limit	Upper limit	p-Value
Solo NMT frequency	0.618	0.408	0.937	0.024
Multi NMT frequency	0.353	0.234	0.532	0.001

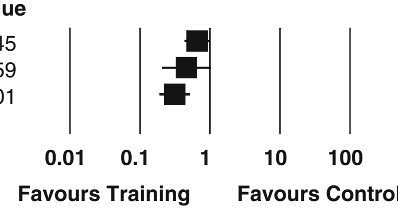
Statistics for each study; Odds ratio and 95% CI

Sub-group Analysis, Random Model

Fig. 4 Subgroup analysis of NMT frequency and anterior cruciate ligament injury in 12 clinical trials. *NMT* neuromuscular training

Variable	Odds ratio	Lower limit	Upper limit	p-Value
Low NMT volume	0.655	0.433	0.991	0.045
Moderate NMT volume	0.461	0.207	1.029	0.059
High NMT volume	0.315	0.190	0.523	0.001

Statistics for each variable; Odds ratio and 95% CI



Sub-group Analysis, Random Model

Fig. 5 Subgroup analysis of NMT volume and anterior cruciate ligament injury in 12 clinical trials. *NMT* neuromuscular training

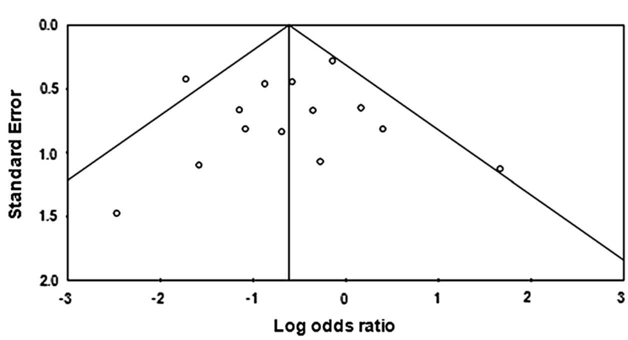


Fig. 6 A trim and fill plot for testing publication bias

implies that longer and more frequent NMT programs demonstrated greater NMT prophylactic effects. Comparing the risk difference between the long and short NMT session, the long NMT session clinical trial groups showed a 26 % lower risk. Similarly, the multi NMT frequency group demonstrated a 27 % lower risk than the single NMT frequency group. In fact, one of the reviewed clinical trials compared the ACL injury rate based on compliance, and more compliant athletes demonstrated significantly less ACL injury risk than those who were less compliant [34]. Similarly, another clinical trial reviewed in this analysis also documented a lower risk of non-contact lower leg injury in the high-compliance group [33]. The results of these studies thus support longer durations of and more frequent NMT interventions for increased prophylactic effect.

4.1 Neuromuscular Training Duration

Breaking down the NMT volume with sub-components, including duration (short vs. long) and frequency (single vs. multi), it appeared that fewer types of NMT exercises were prescribed in the short NMT session studies [19, 26]. This can simply be interpreted that it is difficult to perform many types of NMT exercises in the limited amount of NMT session time, which might have impacted reducing the prophylactic effects of NMT. However, the long NMT session raises a question with regard to practicality. The longer the NMT session duration, the more difficult to implement a NMT program. Two studies that had the longest NMT durations were pre-season programs [16, 29], which may indicate a difficulty in implementing a long NMT program, especially during the in-season schedule. An NMT implementation requires understanding and support from coaching staff, and they may not be supportive of implementing a long NMT program because the long NMT session often results in decreasing actual practice time. The same issue is applied to the NMT frequency, which may result in a reduction in compliance.

4.2 Neuromuscular Training Frequency

The current data regarding NMT frequency need to be interpreted cautiously. All clinical trials that had the single NMT session during the in-season frequently had NMT sessions in the protocols during the pre-season. For instance, two clinical trials [27, 30] had athletes perform preventive NMT 15 consecutive times in the beginning of the season and decreased the NMT frequency to once a week during in-season. Similarly, two other clinical trials employed NMT three times per week during pre-season and reduced the NMT frequency to once a week during the in-season [26, 31]. Therefore, although the current analyses suggested that performing preventive NMT interventions less than 20 min per session once a week during the in-season can reduce 38–39 % of ACL injury risk (Figs. 3, 4), practicing one NMT session per week during the in-season without frequent pre-season NMT workouts is less likely to demonstrate prophylactic effects on ACL injury reduction. Another meta-analysis that evaluated the effectiveness of NMT programs in lowering ACL incidence in female athletes reported that combined pre-and in-season NMT intervention is the most effective process to reduce incidence of ACL, rather than either pre- or in-season NMT programs alone [35].

Potential benefits of performing pre- and in-season NMT interventions were evidenced by two clinical trials reviewed in this project. A clinical trial with a cluster randomized controlled design performed by Gilchrist et al. [32] recorded similar ACL injury rates between athletes in intervention and control groups in the first half of the soccer season. However, during the second half of the season, no ACL injury was observed among athletes in the intervention group, but five ACL injuries were noted in the control group. Similarly, in a clinical trial conducted by LaBella et al. [25], no ACL injury was documented in basketball athletes in the intervention group during the second half of the regular season. These studies support that it takes a certain amount of time for athletes to adopt the patterns of NMT performance. Physiologically, muscle activation enhancement was not observable after 3 weeks of physical training, but was seen after 6 weeks [36]. More interestingly, one study reported that strength gains to the trunk and the lower extremities were slower than that to the upper extremities [37]. In addition to physiological alterations, motor skill adaptations and transformations in actual performance during practice and game situations may require a longer time period. Thus, considering the necessary time for athletes to attain the NMT skills, it is logical to provide NMT during the pre-season.

4.3 Neuromuscular Training Volume

The NMT volume analysis, which consists of low-, moderate-, and high-volume categorizations and is a combination of NMT session and NMT frequency during the in-season, also supports the inverse dose-response association. The observed inverse dose-response association is that the greater the NMT volume, the greater the prophylactic effect. The statistically greater prophylactic effects were found in the higher NMT volume group compared with the lower NMT volume group. The high NMT volume group may reduce ACL injury risk by 68 %, whereas the risk reduction in the moderate and low NMT volume groups were 54 and 44 %, respectively. The 24 % risk reduction differences between the high and low NMT volume groups can be attributed to dosage (NMT duration and frequency) difference. The results of the NMT volume analysis provide a meaningful clinical implication. The current analysis suggests that 68 % of non-contact ACL injuries can be avoided if a preventive NMT program of more than 20 min duration and multiple sessions per week is employed in female athletes (Fig. 5) [38–42].

A majority of those who experience ACL rupture undergo reconstructive surgery, but still experience early osteoarthritis (OA) changes within 8–15 years after reconstructive surgery [43–46]. Research on knee-related quality of life in these individuals [44] has found that if a female athlete has an ACL injury during her middle teens, premature OA may be present at the age of 30 years or even earlier. Hence, performing NMT may provide substantial future health benefits for females. Female athletes can potentially reduce risk for those negative consequences, which, in turn, holds more opportunities for maintaining a physically active lifestyle.

Several recent studies reported on the significance of NMT dosage using a compliance measurement. Using a prospective cluster randomized controlled design, Soligard et al. [47] examined an association between NMT compliance and soccer-related injuries. Comparing acute and overall soccer injuries with compliance rates in a tertile fashion (high, intermediate, and low), athletes with high compliance rates showed a 35 % lower risk than those with intermediate compliance rates in overall soccer-related injuries. Similarly, in terms of acute soccer injuries, athletes with high compliance rates experienced a 39 % risk reduction in relation to athletes with intermediate compliance rates. In addition, high NMT compliance rates and low injury risks were also reported by Sugimoto et al. [48]. The authors also categorized the compliance rates in a tertile fashion (high, moderate, and low) and examined the association between ACL injury rates in six clinical trials. The analysis identified that the moderate NMT compliance clinical trials had a 3.1 times greater risk of experiencing ACL injuries than high-compliance clinical trials. Similarly, the low-compliance clinical trials demonstrated a 4.9 times greater ACL injury risk than high-compliance clinical trials. Both analyses documented the impact of the NMT dosage through compliance assessment in relation to athletic injuries, which supports the result of the current subgroup analysis.

4.4 Limitations

For the subgroup analysis for the dosage effect, the length of the NMT programs was considered as a variable. However, the NMT length within each clinical trial was significantly diverse, ranging between 6–8 weeks [16, 29, 31] to 4–7 months [17–20, 25–27, 30–34]. Thus, the current project could not find a meaningful cut-off point for the NMT length subgroup analysis. However, most clinical trials [17–20, 25–27, 30–34] used the NMT as a warm-up and the number of ACL injuries were counted during the competitive athletic season. Therefore, the longer the length of NMT and competitive seasons, the greater numbers of ACL injuries were likely to be recorded. Hence, the current project focused on aspects within the NMT length within each clinical trial.

In the NMT volume analysis, the moderate NMT group demonstrated fairly wide CIs compared with high and low NMT volume categorizations (Fig. 5). This is mainly explained by a small number of subjects in this group compared with the other two groups. The other two groups had more than 3,500 subjects in both intervention and control groups, but the number of subjects in the moderate NMT group in each arm did not reach 2,000, likely accounting for the wide CIs.

Seven of the 14 included clinical trials [25, 27, 29, 30, 32–34] were rated as level I (high-quality individual randomized control trial), and the remaining seven clinical trials [16–20, 26, 31] were rated as level II (lower-quality clinical trial and cohort study). Randomization is known as an effective method to reduce potential bias. Therefore, if more clinical trials were randomized, the outcome of each cohort clinical trial might have differed, and the evidence would be more substantial. Thus, more trials of this nature would be valuable. However, in order to present the best available evidence, the presented meta-analysis (Fig. 1) was performed based on clinical trials found under a comprehensive and systematic literature search.

Although subject populations were homogenous (young female athletes), diversity was observed in the sports: soccer, handball, basketball, and floorball. In addition subjects' ages and NMT programs varied among clinical studies. It was challenging to differentiate the reviewed clinical trials further based on the sports, ages, and types of NMT. Thus, the prophylactic effects demonstrated by the current analyses may vary by sport, age, and given NMT programs.

5 Conclusion

In order to find potential aspects to enhance prophylactic effectiveness of NMT, a series of subgroup analyses were performed, which found an inverse dose-response effect: the higher the NMT volume, the greater the prophylactic effectiveness of the NMT program and more benefit for female athletes in ACL injury reduction. Specifically, about 70 % of ACL injury was avoided if preventive NMT was performed a total of more than 30 min per week during the in-season. Since implementation of NMT requires the understanding and cooperation of coaching staff, it may be more realistic and applicable to perform NMT multiple times per week instead of one 30-min session a week, especially during the in-season. The current analysis suggests that the desirable NMT duration is longer than 20 min per session. In addition, a few reviewed clinical trials incorporated a substantial amount of NMT sessions during pre-season rather than just during in-season. Also, several clinical trials noted more ACL injuries in the beginning of competitive seasons. Because of these two factors, performing preventive NMT during both pre- and in-seasons is suggested. The current analysis was rated as evidence level A in the SORT evidence category. Hence, the results of this report encourage healthcare practitioners to apply preventive NMT to female athletes to minimize the likelihood of an ACL injury, which should promote a physically active and healthy lifestyle in young females' lives.

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