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**Non-local acute passive stretching effects on range of motion in healthy adults:
A systematic review with meta-analysis**

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Running Title: Global stretching effects

Abstract

Background: Stretching a muscle not only increases the extensibility or range of motion (ROM) of the stretched muscle or joint but there is growing evidence of increased ROM of contralateral and other non-local muscles and joints.

Objective: The objective of this meta-analysis was to quantify crossover or non-local changes in passive ROM following an acute bout of unilateral stretching and to examine potential dose-response relations.

Methods: Eleven studies involving 14 independent measures met the inclusion criteria. The meta-analysis included moderating variables such as sex, trained state, stretching intensity and duration.

Results: The analysis revealed that unilateral passive static stretching induced moderate magnitude (standard mean difference within studies: SMD: 0.86) increases in passive ROM with non-local, non-stretched joints. Moderating variables such as sex, trained state, stretching intensity, and duration did not moderate the results. Although, stretching duration did not present statistically significant differences; greater than 240-seconds of stretching (SMD: 1.24) exhibited large magnitude increases in non-local ROM compared to moderate magnitude improvements with shorter (<120-seconds: SMD: 0.72) durations of stretching.

Conclusion: Passive static stretching of one muscle group can induce moderate magnitude, global increases in ROM. Stretching durations greater than 240 s may have larger effects compared with shorter stretching durations.

Key Points: Non-local (crossover or global) stretching effects from unilateral **passive** stretching can induce moderate magnitude ROM increases. This increased **non-local** ROM was not modified by the participant's trained state, sex or stretching intensity. Although not statistically significant, there may be a trend for greater ROM improvements with longer durations of unilateral stretching.

1.0 Introduction

There is an abundance of literature demonstrating stretch-induced acute increases in joint range of motion (ROM) [1-4]. Improvements in ROM permit more expansive movements with less resistance [2], enhance longer duration stretch-shortening cycle activity (prolonged amortization or transition phase) performance (i.e. longer distance running, rebound chest press and others) [5, 6] and have been reported to enhance muscle force output at longer muscle lengths [7-10], which is typically the environment where many musculotendinous injuries occur [1]. Moreover, from an injury prevention perspective, increased ROM has been shown to reduce the incidence of musculotendinous injuries specifically with explosive, high speed, and change of direction activities [1]. Mechanisms underlying the enhanced acute ROM have been attributed to an increased stretch tolerance, neural inhibition, thixotropic properties (i.e. decreased viscoelasticity) and muscle and tendon architectural modifications (i.e. changes in tissue compliance, stiffness, fascicle angles and rotation among others) [11-22]. Subsequently, knowledge of the training methods that can be used to optimise ROM are of key importance.

Crossover, or non-local augmentation of ROM has also been reported when the stretching of one muscle produces an increased ROM in a homologous (crossover) or heterologous non-stretched muscle or joint [23-35]. Such a global or systemic response to stretching would have important implications with training and rehabilitation, particularly when a unilateral injury prevents training or activity. For example, prior to a rehabilitation exercise, an individual can perform unilateral stretching to access a greater contralateral ROM when performing the activity without fear of further injuring the affected muscles or tendons. The genesis of non-local stretching effects research originated with studies examining crossover or non-local muscle fatigue [36-47]. The term: non-local muscle fatigue was incorporated to indicate a temporary deficit in performance

of non-exercised homologous and heterologous muscle groups that could be located contralateral, or ipsilateral, as well as inferior or superior to the fatigued muscle groups [45]. The proposed mechanisms of non-local muscle fatigue have been ascribed to neural inhibition, biochemical (i.e. metabolite distribution of lactate, H^+ , K^+ ions and others), biomechanical (trunk fatigue impairing stability), and psychological (i.e. mental energy deficit) factors [45]. Based on non-local muscle fatigue effects, some researchers were intrigued to examine whether similar global effects would occur following unilateral acute stretching. Clark [29] published the earliest evidence using six unilateral hamstrings static stretches of six seconds each and reported a 14.4% improvement in the straight leg raise ROM. The 10 other studies investigating non-local stretching effects have just been published in the last five years (2016-2020). As the increased acute ROM of a non-stretched muscle cannot be attributed to peripheral or local mechanisms (i.e. thixotropic or architectural modifications), the non-local ROM changes would illustrate the extent of global mechanisms. Unlike non-local muscle fatigue [45], there would be little accumulation and distribution of metabolites, and a reduced chance of trunk muscle or core fatigue. Hence, non-local stretching effects would more likely be attributed to neural inhibition or psycho-physiological (i.e. increased stretch or pain tolerance) factors [1].

Furthermore, there are conflicts in the literature regarding variables that could moderate the effectiveness of stretching on ROM. For example, a variety of stretch intervention studies have shown similar improvements in ROM of the stretched limb or joint with 15 vs. 30 s [48], 120 vs. 240 s [49], 3.5 vs. 7 vs. 10.5 min [50] of static stretching. On the other hand, greater increases in ROM were found by Roberts and Wilson [51] with 15 s versus 5 s duration stretches, Bandy and Irion [52] suggested that 30–60 s of static stretching was more effective than 15 s, with other researchers also suggesting greater than 30 s of static stretching to achieve the greatest ROM [53,

54]. It is unknown if the duration of unilateral stretching impacts non-local ROM. The effect of unilateral stretching intensity on non-local ROM, which could impact sensory afferent neural influences or psychological (i.e. stretch or pain tolerance) factors also needs to be evaluated in future studies. The influence of stretching intensity on the stretched limb's ROM is also contradictory with evidence showing no substantial ROM differences when comparing stretching at submaximal intensity to maximal or near maximal ROM or discomfort [55-57] versus evidence of greater ROM when implementing low force prolonged static stretching [58,59]. Again, there is no information on non-local responses to stretch intensity. In addition, there are a number of other possible moderating variables that could impact non-local ROM. For example, there are very few studies that recruited trained individuals and no studies that have used only female participants and thus the trained state and sex could play a role.

With no published systematic reviews or meta-analyses regarding the extent (magnitude) of stretching on non-local ROM, the objective of this meta-analytical review was to examine the literature to determine the relative effect of varying unilateral muscle stretching durations upon non-stretched muscles or joint passive ROM in healthy untrained and trained adults under the age of 40 years, with the goal of strengthening the mechanistic underpinnings of acute stretching. We were additionally interested in the effect of moderating variables such as unilateral stretch duration, intensity, trained state, and participants' sex. Based upon previous findings reporting the effects of acute stretching durations on ROM [51, 52, 53, 54], we hypothesized that longer durations of acute stretching would induce greater increases in non-local joint ROM in healthy untrained and trained young adults. Furthermore, based on prior studies [55-57], it was also hypothesized that stretch intensity would not impact non-local ROM.

2.0 Methods

2.1 Search strategy

A literature search following Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-P) review guidelines was performed by two co-authors (SA and SHA) separately and independently using PubMed, Scopus, SPORTDiscus, Web of Science, Cochrane, and CINHAL Plus databases. The topic was searched using a Boolean search strategy with the operators “OR” and “AND” and a combination of the following title keywords: stretch, stretching, flexibility, range of motion, non-local, unilateral, contralateral, ipsilateral, crossover, or remote (Figure 1). Researchers’ personal computer databases were also examined for related articles. Related articles were found from 1999 to July 2020 (no date restrictions imposed). The selected articles were also cross referenced by the authors to identify relevant studies that might have been overlooked in the database search. In selecting studies for inclusion, a review of all relevant article titles was conducted before an examination of article abstracts and, then, full published articles. Only peer-reviewed articles were included in the meta-analysis.

2.2 Data extraction

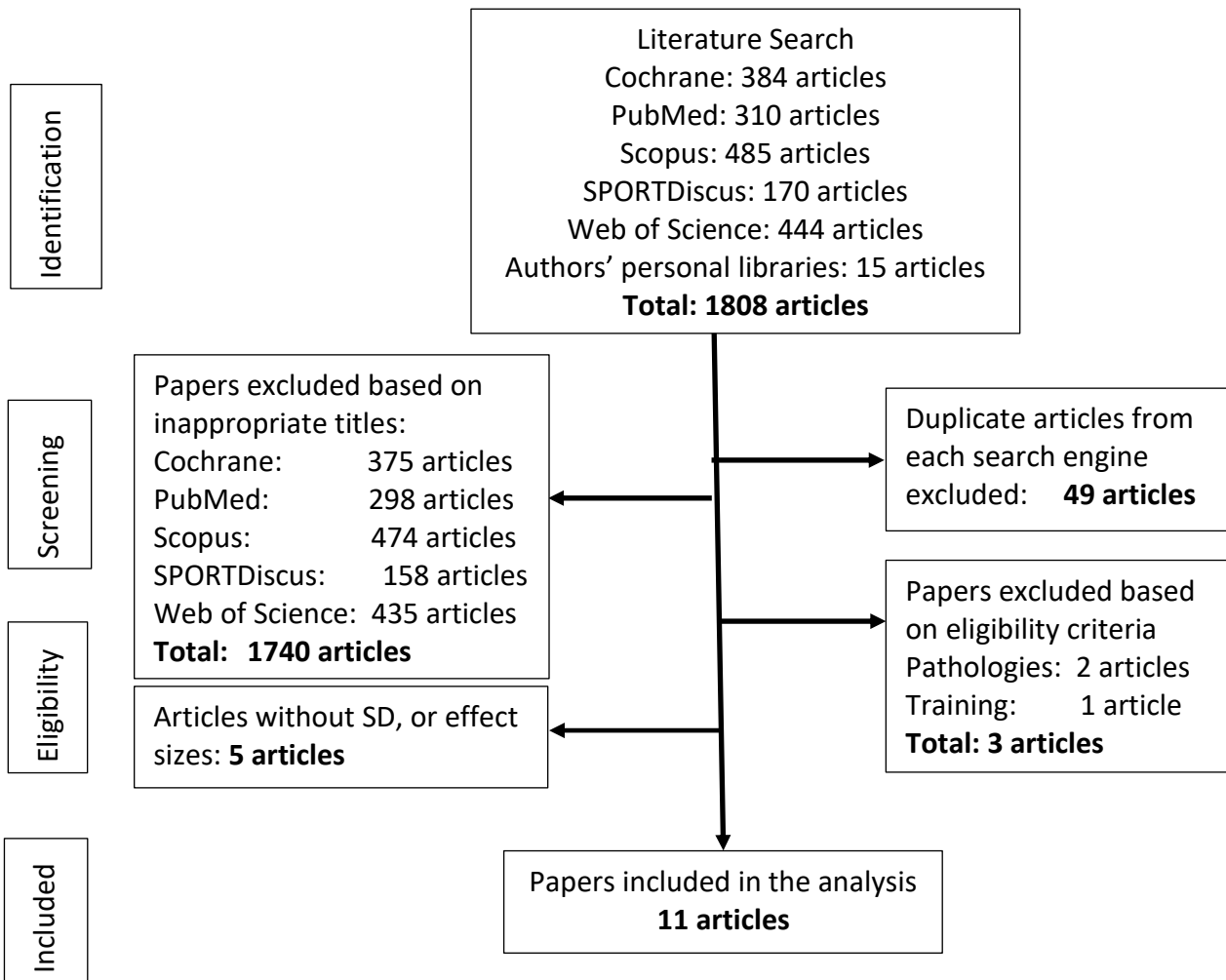
Data were extracted from gathered articles with a form created in Microsoft Excel. Where required data were not clearly or completely reported, article authors were contacted for clarification. In case authors did not respond to our queries, the respective dataset was not considered for further analysis.

2.3 Inclusion and exclusion criteria (study selection)

Articles investigating non-local stretching were included if they fulfilled the following selection criteria: the study 1) was a randomized controlled trial or a controlled trial; 2) included a measure of acute (not cross-education training studies) pre- and post-stretching homologous or heterologous muscle or joint ROM, 3) was published in a peer-reviewed journal (abstracts and

unpublished studies were excluded), 4) was published in English before July, 2020; and 5) the study participants were healthy, untrained, recreationally active, or trained individuals under the age of 40 years. Furthermore, non-exercised muscle group(s) could not be the antagonists to the stretched muscle groups (e.g., knee extensors and flexors), as movement of the stretched muscle could stretch the antagonist muscle, thus distorting the effect we desired to examine. Studies were excluded if means and standard deviations, or effect sizes were not available.

Figure 1: PRISMA flow chart illustrating different phases of the search and study selection using the following title based nomenclature: stretch, stretching, flexibility, range of motion, non-local, unilateral, contralateral, ipsilateral, crossover, or remote.



2.4 Systematic review analysis

Meta-analytical comparisons were carried out in RevMan version 5.3 (The Nordic Cochrane Centre. Cochrane Collaboration. 2014. p. 1–43). Means and standard deviations for a measure of joint range of motion was used to calculate an effect size. The outcome variable (ROM) was chosen based on a logically defensible rationale, an accepted method of study-inclusion justification in a meta-analysis [60]. To analyse the collected data, the inverse-variance random effects model for meta-analyses was used because it allocates a proportionate weight to trials based on the size of their individual standard errors [61] and facilitates analysis whilst accounting for heterogeneity across studies [62], a common characteristic of intervention-based research. The analysis encompassed a primary analysis (all studies combined) as well as an evaluation of moderating variables such as stretch duration, intensity, participants' trained state and sex. We presented effect sizes alongside 95% confidence intervals (CI) and these were interpreted using the conventions outlined for standardised mean difference by Hopkins et al. [63] (<0.2 = trivial; 0.2-0.6 = small, 0.6-1.2 = moderate, 1.2-2.0 = large, 2.0-4.0 = very large, >4.0 = extremely large).

To gauge the degree of heterogeneity amongst the included studies, the I^2 statistic was calculated. This represents the percentage of variation across studies that is due to heterogeneity as opposed to chance [64]. Low, moderate, and high levels of heterogeneity correspond to I^2 values of 25%, 50% and 75% respectively; however, these thresholds are considered tentative [65]. The X^2 (chi square) assesses if any observed differences in results are compatible with chance alone. A low P value, or a large chi-squared statistic relative to its degree of freedom, provides evidence of heterogeneity of intervention effects beyond those attributed to chance [63].

2.5 Assessment of risk of bias

The Physiotherapy Evidence Database (PEDro) scale was used to assess the risk of bias and methodological quality of the included studies (Table 1). This scale evaluates internal study validity on a scale from 0 (high risk of bias) to 10 (low risk of bias). Two reviewers independently rated each study. Any ratings that yielded different results were further adjudicated by a third reviewer. This rating was then used in the risk of bias scale. A median score of ≥ 6 represents the threshold for studies with a low risk of bias [66]. Furthermore, figures 2-6 show symmetric funnel plots, which illustrate the absence of publication bias in the observed studies.

3.0 Results

3.1 Study selection

In total, eleven studies met the inclusion criteria and were included in the meta-analysis (Table 2). They comprised 14 experimental groups. Mean study participant characteristics are provided in Table 3. The PRISMA flow diagram illustrating the number of studies excluded at each stage of the systematic review and meta-analysis is shown in Figure 1. As only two studies examined the effect of unilateral stretching on heterologous muscle groups, it was not possible to statistically analyze heterologous versus homologous ROM responses.

Table 1: Pedro scale analysis of articles

Study	1	2	3	4	5	6	7	8	9	10	11	Total
Behm et al. 2016 [23]	Y	N	Y	Y	Y	N	N	N	Y	Y	Y	7
Behm et al. 2019 [24]	N	N	N	Y	Y	N	N	N	Y	Y	Y	5
Caldwell et al. 2019 [25]	Y	N	N	Y	N	N	N	N	N	Y	Y	4
Caldwell et al. 2019 [26]	Y	Y	Y	Y	Y	N	N	Y	Y	Y	Y	9
Ce et al. 2020 [27]	Y	N	N	Y	N	N	N	Y	N	Y	Y	5
Chaouachi et al. 2017 [28]	N	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Clark et al. 1999 [29]	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	10
de-la-Cruz Torres et al. [30]	Y	Y	Y	Y	Y	Y	Y	N	N	Y	Y	9
Killen et al. 2018 [31]	Y	Y	N	Y	N	N	N	Y	Y	Y	Y	7
Lima et al. 2014 [32]	Y	N	N	Y	N	N	N	Y	Y	N	Y	5
Whalen et al. 2019 [33]	Y	Y	N	Y	Y	Y	N	Y	Y	Y	Y	9
Wilke et al. 2016 [35]	Y	N	N	Y	N	N	N	Y	Y	Y	Y	6
Mean												6.57
Median												6.5
Mode												7.0

Y: Yes, N: No

PEDro scale criteria

1. Eligibility criteria were specified.
2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received) .
3. Allocation was concealed.
4. The groups were similar at baseline regarding the most important prognostic indicators.
5. There was blinding of all subjects.
6. There was blinding of all therapists/researchers who administered the therapy/protocol.
7. There was blinding of all assessors who measured at least one key outcome.
8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups.
9. All subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by “intention to treat”.

10. The results of between-group statistical comparisons are reported for at least one key outcome.

11. The study provides both point measures and measures of variability for at least one key outcome.

Study	Age	M/F	Trained state	Stretched muscle group	Reps / sets	Duration (s)	Volume (s)	Rest (s)	Intensity	Tested, non-stretched muscle group	%Δ
Behm et al. 2016 [23]	27.0 ±7.0	8/4	RT	hip adductor SS	10	30	300	15	70-90% POD	Shoulder	8.16
Behm et al. 2019 [24]	19-30	14M	PA	Quads + Hams SS	8	30	240	-	100% POD	Contra Hip & Quads	3.49
Caldwell et al. 2019 [26]	22.6 ±2.7	4/6	H RA	Hams & Quads SS	3	30	90	15	100% POD	Contra Hams & Quads	5.90
Caldwell et al. 2019 [26]	20.5 ±0.8	4/6	H RA	Hams and Quads SS	6	30	180	15	100%POD	Contra Hams & Quads	6.36
Ce et al. 2020 [27]	22.0 ±3.0	21M	H	Quads SS	5	45	225	15	80-90% POD	Contra Quads	11.00
Chaouachi et al. 2017 [28]	18.0 ±2.0	14M	Rowers	Hip flexion SS	8	30	240	20	POD	Contra Hip flexion	4.99
Clark 1999 [29]	25.6 ±2.8	45/15	H	Hams SS	6	6	36	5	POD	Straight Leg Raise	14.36
Clark 1999 [29]	25.6 ±2.8	45/15	H	Hams SS	1	120	120	-	POD	Straight Leg Raise	8.24
de-la-Cruz Torres et al. 2020 [30]	22.7 ±4.5	10/10	H	Hams SS	3	30	90	-	POD	Straight Leg Raise	17.28
Killen et al. 2017 [31]	M:26±3, F:27±2	13/10	PA	Hams SS	10	30	300	30	100%POD	Contra Hams	13.60
Lima et al. 2014 [32]	M:25±3, F:22±3	7/7	H UT	PF SS	6	45	270	15	70-90% POD	Contra PF	30.20
Whalen et al. 2019 [33]	M: 21.7±1.5 F:20.5±1.3	7/7	H	Hams SS Hams PF	3	30	90	30	100%POD	Contra Hams	0.08
Wilke et al. 2016 [35]	36±13	32/31	H	Hams PF SS	3	30	90	-	mild POD	Cervical flex/extension	5.0
Wilke et al. 2016 [35]	36±13	32/31	H	Control	-	-	-	-	-	Cervical flex/extension	0.4

Table 2: Individual study characteristics:

Abbreviations and Acronyms: Contra: contralateral, ES: effect size, Flex/ ~~exten~~: flexion / extension, H: healthy, Hams: hamstrings, M/F: # of Male/Female participants, PA: physically active, PF: plantar flexors, POD: point of discomfort, Quads: quadriceps, RA: recreationally active, reps: repetitions, RT: resistance trained, SS: static stretch, UT: untrained

Table 3: Study characteristics: Mean± standard deviation values

Age (yrs)	Males (n)	Females (n)	Trained state	Unilateral Stretched muscles	Tested, non-stretched muscles	Reps/Set	Duration (s)	Volume (s)	Rest (s)	Intensity
18-27	18.3±13.9	12.9±9.1	HUT: 5 PA: 4 RT: 1 Rowers: 1	Hams: 5 Quads, PF, hip adductors: 1 each	Hams: 6 Quads: 3 Shoulders, PF: 1 each	5.5±2.7	37.4±25.4	174.7±88.8	17.7±7.5	POD: 6 70-90% POD: 3 Mild POD: 4

Abbreviations and Acronyms: Hams: hamstrings, HUT: healthy untrained, (n): number of participants, PA: physically active, PF: plantar flexors, POD: point of discomfort, Quads: quadriceps, RT: resistance trained, (yrs): years.

3.2 Primary analysis

For the primary analysis, there was a moderate, significant effect of **passive** static stretching on **non-local** ROM (Effect size: ES = 0.86 [95%CI: 0.51, 1.20], Z = 4.83 [p < 0.01]). Between-study heterogeneity was moderate and significant (I² = 66% [p < 0.01]). These results are displayed in Figure 2.

3.3 Effect of moderator variables

The results of the moderator analysis are displayed in Table 4. Differences between subgroups were non-significant with low heterogeneity. For the moderator ‘trained state’, moderate magnitude effect sizes were found in trained (1.14 [95%CI: 0.26, 2.01]) and untrained (0.79 [95%CI: 0.36, 1.21]) participants (Figure 3). For the moderator ‘stretch intensity’, ‘maximal’ stretching (0.81 [95%CI: 0.09, 1.53]) had a marginally lower effect size than ‘submaximal’ (0.99 [95%CI: 0.61, 1.37]) (Figure 4). For stretching duration, >240 seconds per stretch (1.24 [95%CI: 0.46, 2.02]) resulted in a large magnitude effect size which exceeded the moderate magnitude effects found with 120 to 240 seconds (1.03 [95%CI: 0.18, 1.88]) and <120 seconds (0.72 [95%CI: 0.35, 1.09]) (Figure 5). For the moderator ‘sex’, it was not possible to compare a male group to a female group so, instead, a male group was compared to a combined male and female group. For this moderator variable, there was a marginally greater effect in males (1.10 [95%CI: -0.04, 2.24]) than in combined males and females (0.79 [95%CI: 0.44, 1.14]), though both effect sizes were of moderate magnitude and there was an imbalance in the amount of studies allocated between the subgroups (Figure 6).

Figures 2-6: Funnel plots for main analysis and moderator variables

Table 4 Moderator analyses for effect of acute stretching on non-local range of motion in healthy adults

4.0 Discussion

The major finding of this meta-analysis was that unilateral, acute, **passive**, static stretching induced moderate magnitude increases in **non-local** (non-stretched) joint ROM in healthy young adults (Figure 2). Moderating variables such as trained state, stretching intensity, and sex did not modify the results (Figures 3,4,6). Although, stretching duration did not result in statistically significant differences; greater than 240-seconds of stretching exhibited large magnitude increases in **non-local** ROM compared to only moderate magnitude improvements with lower (<240- and <120-seconds) durations of stretching (Figure 5).

4.1 Moderating Variables: Trained state

There was no statistically significant difference between the **non-local** stretching response with both trained (SMD: 1.14) and untrained (SMD: 0.79) groups, demonstrating a mean, moderate magnitude increase in **non-local** ROM (Figure 3). While the difference was not statistically significant, the chance of reporting a type II, false negative finding could be possible with only three studies conducted with trained individuals in the analysis. Although trained individuals might be expected to achieve greater ROM of a stretched muscle due to training-induced morphological adaptations to muscles and tendons [22, 49], the **non-local** response may be more dependent on psycho-physiological responses and thus may not exhibit trained state differences. More research is needed to ensure there are no type II errors in an analysis due to insufficient number of studies.

4.2 Moderating Variables: Stretching Intensity

There was no statistically significant effect of **passive** static stretching intensity with both maximal (SMD: 0.81) and submaximal (SMD: 0.99) stretching intensities showing moderate magnitude **non-local** effects (Figure 4). This finding is in accord with studies examining varying stretch intensity effects on the stretched muscle or joint. For example, studies using 50 and 85%

of point of discomfort (POD)[49], initial POD, maximum POD and 120% of maximum POD [67], initial POD and near maximal POD [68] or 4 weeks of low or high intensity stretch training [69], all reported similar increases in ROM. Although classified as submaximal for this analysis, most studies with this classification in Table 2 had participants stretch at 70-90% of maximal intensity or tolerance. Since possible differences in the degree of discomfort between 70-90% and maximal intensity stretching may elicit minimal differences in pain perception, the stretching intensities used in these studies could have elicited similar psycho-physiological responses.

The psycho-physiological ability to cope with stretch discomfort or pain may influence the global effects of static stretching and illustrate a possible non-local flexibility mechanism. The concept of increased stretch tolerance suggests the musculotendinous unit can tolerate greater stress without a change in tension for a given length [14, 16]. Muscle sympathetic nervous activity has been shown to be elevated with stretching [72], facilitating stretch reflexes [73] influencing both the exercised and non-exercised muscles [74]. Guissard and Duchateau [75], indicated that joint ROM is highly influenced by the muscle resistance caused by tonic reflexes. Roatta et al. [76] provided evidence for sympathetic-induced increases in motor unit discharge frequency and reduced twitch $\frac{1}{2}$ relaxation time demonstrating adrenergic stimulation of muscle fibre contractility. Hence, sympathetic-induced (fight or flight) reflexive and motor unit-induced effects on muscle tonicity could increase resistance to global muscle extensibility.

While **passive** static stretching may not seem excessively dangerous, the objective of pain perception is to alert the individual to potential threats or damage [70] and thus excite the sympathetic nervous system [71]. We speculate, that in the case of sustained stretching near or at the POD, the individual would soon sense that the discomfort of stretching was not a serious threat or harm and the fight or flight response (increased sympathetic excitation) would be downregulated

over time to allow the individual to relax and perhaps extend the muscle even farther (greater stretch tolerance). This cortical perceived lack of threat or injury resulting in decreased sympathetic activation (neural and endocrine responses) and increased stretch tolerance should translate to a global response (increased non-local muscle or joint ROM). The sympathetic nervous system responses affect the entire body and are not specific to a single muscle or region [72, 79] and thus would impact non-local muscles [74].

In addition, increased global stretch tolerance might be related to global pain modulatory systems such as diffuse noxious inhibitory control (DNIC) [80-82]. Stretching to the POD can induce some prolonged (i.e. 30-60 seconds) mild or moderate pain. DNIC is activated by nociceptive (pain) stimuli (i.e., mechanical stress) [80-82]. The nociceptive receptor activity is transmitted to multi-modal, dynamic range convergent cortical neurons in the subnucleus reticularis dorsalis where it can suppress pain transmission monoaminergically [80-82], reducing pain perception not only at the painful location but also globally [82, 83]. DNIC suppresses pain sensitivity with the widespread distribution of monoamines such as endorphins, enkephalins and other compounds to contribute to global analgesia [82,83], thus contributing to greater non-local stretch or pain tolerance. Stove et al. [84] demonstrated this global analgesia/increased non-local stretch (pain) tolerance effect by providing a painful cold pressor test to the hand and wrist and found an increase in passive knee extension ROM.

4.3 Moderating Variables: Stretching duration

Similar to the trained state variable, there was no statistically significant difference between low (<120-s), moderate (<240-s) and long (>240-s) duration stretching interventions (Figure 5). However, there was a SMD numerical trend for increasing effect sizes with increasing stretch durations, which agrees with the findings of Reid et al. [85], who reported greater ROM with 120

s versus 60 s, and both durations had greater ROM than 30 s of static stretching. The statistically significant ROM differences associated with stretch duration reported by Reid et al. [85] might be attributed to the augmented benefits of performing the stretching within a full warm-up including prior aerobic activity and post-stretch dynamic activities. While low [26, 29, 30, 33, 35] and medium [24, 26, 27, 28] duration, unilateral stretch interventions demonstrated moderate (0.72 and 1.03 respectively) magnitude increases in **non-local** ROM, long (1.24) duration stretches [23, 31, 32] provided increasingly larger magnitude non-local ROM increases. With a low number of studies (short: 6 studies, medium: 4 studies, long duration: 3 studies), the interpretation of the statistics is fraught with difficulties. Both the medium and long duration stretch durations had one study each with an outlier effect size that was substantially higher than the other 2-3 studies in the medium and long duration groups respectively. If the numerical differences do represent a trend, it could be speculated that the longer duration of discomfort might contribute to an augmented stretch (pain) tolerance. However, once again, more stretch duration studies are needed to strengthen statistical interpretations.

The aforementioned role of sympathetic stimulation on non-local ROM can originate not only from cortical efferents but also peripheral afferents. Thus, another mechanism that might impact changes in non-local ROM are myofascial and skin sensory receptors [86,87], that are sensitive to skin stimulation, tangential forces and lateral stretch [88]. These exteroceptive (E-) reflexes possess multi-synaptic innervations to motoneurons [89, 90], that inhibit sympathetic excitation (decrease muscle tone) [91]. Furthermore, stretching can activate skin and joint receptors, which also project to the somatosensory cortex and thalamus, which could also affect motor output from the primary motor cortex [92]. However, exteroceptive reflex effects cease within seconds after stretching and human [75] and animal (cat) studies [93-95], have suggested

that exteroceptive receptors' inhibition contribute only a minor component to ROM increases with larger amplitude stretches.

Prolonged **passive** static stretching (i.e. 30-s or more) can impede motoneuron spindle reflexive (excitatory) activity [1, 2, 96, 97], which project to spinal motoneurons as well as to the somatosensory and the primary motor cortex [101-103]. Extensive transcollosal and inter-cortical projections have been proposed as a major mechanism underlying cross-education training effects [98-100]. A lack of stretch-induced changes in corticospinal excitability have been reported when testing muscles at rest, [104-106], with MVCs [104] and 20% MVC [107]. In contrast, Opplert et al. [108] reported motor evoked potential amplitude increases with a 30% MVC after 5 sets of 20 s of passive stretching. Hence, with five of six stretching-related studies demonstrating no motor evoked potential changes, the inhibitory effects of passive stretching on corticospinal excitability with non-local stretching ROM changes is likely to be minimal. Similarly, the cortical silent period, which provides insight into GABA_B inhibitory interneurons effects on intra-cortical inhibition reveal no changes during MVC [104], 30% [108] and 20% [107] MVCs after passive stretching. Thus, with a lack of stretching-induced changes in corticospinal excitability or intra-cortical inhibition, the role of stretch reflex-induced neural inhibition on non-local or global stretching effects and performance is quite likely trivial compared to stretch tolerance (reduced sympathetic excitation and global pain modulatory systems) mechanisms.

A further contributing mechanism to non-local increases in ROM might be the influence of myofascial chains. As myofascia envelopes all muscles, it has been postulated that they provide an extensive network of myofascial chains or meridians [109]. Animal [110, 111] and human cadaveric studies [112-114], demonstrate that fascia can alter its stiffness and transfer stress to adjacent structures. The force transferability of myofascial chains may occur through longitudinal

[115, 116] and spiral (oblique) [117] lines as well as with transversal orientations to synergists and antagonists [118-121]. Wilke [34] suggested that myofascial and muscle strain can be transferred from remote body regions promoting global connectivity. However, the extent of these transfer effects has been debated. Krause et al. [122] suggested that fascial strain is transferred primarily to neighbouring skeletal muscles. The increased cervical ROM after hamstrings [34] and gastrocnemius [35] stretching was ascribed to fascial longitudinal and spiral lines and suggests the possible substantial range of these myofascial chains. However, as Wilke did not directly measure any fascial structural changes, the non-local effects could possibly be due to stretch tolerance or reduced sympathetic excitation, without fascial chain contributions. Even with the acceptance of myofascial chains or meridians, the force transfer is primarily distal to proximal or vice versa (i.e. stretch the hamstrings and increase cervical ROM) and thus longitudinal or spiral chains would not likely contribute substantially to an increased extensibility of a contralateral homologous limb muscle (i.e. hamstrings to hamstrings). Hence myofascial chains may contribute to the longitudinal transfers of myofascial extensibility to improve remote ROM, but probably are not major contributing factors outside the longitudinal and spiral lines. More research is needed to verify these assumptions.

4.4 Moderating Variable: Sex Differences

This meta-analysis did not show statistically significant differences between studies involving only men (SMD: 1.1) versus studies using both men and women (SMD: 0.79), with both groups exhibiting moderate or near moderate magnitude improvements of **non-local** ROM (Figure 6). However, there is evidence in the research for sex differences in stretch tolerance. Marshall and Siegler [123] reported no sex differences in musculotendinous passive stiffness, but females showed greater hamstrings extensibility and lower pain scale scores. Similarly, Hoge et al. [124]

did not find any sex differences in passive stiffness, although females demonstrated greater flexibility. Therefore, the generally greater flexibility of females over males may be attributed to higher female stretch pain tolerance [125]. Nonetheless, this lack of sex difference finding should be viewed with caution as this analysis compared studies that utilized men compared to studies that recruited both men and women. There were no comparative studies that incorporated only women participants.

4.5 Study limitations

We acknowledge that this meta-analysis has some limitations that warrant discussion. First, the overall number of identified studies to be included in the quantitative analysis is rather small (11 studies with 14 experimental groups), which could impact the moderator analyses. However, with reference to the Cochrane Handbook for Systematic Reviews (The Nordic Cochrane Centre. Cochrane Collaboration. 2014. p. 1–43), this number is large enough to aggregate findings in the form of a meta-analysis. In addition, this is the first meta-analysis on non-local acute stretching effects on range of motion in healthy adults, which is why we are confident that this manuscript will advance our knowledge in this relatively new area of research. Second, a large variety of outcome measures assessed ROM in the included studies. This provided heterogeneity in the form of I^2 values ranging between 0-68%. Yet, this range is still below the critical cut-off of 75%. It would also have been interesting to compare heterologous versus homologous ROM responses to unilateral stretching, however there were only two studies that examined heterologous responses [23, 35]. Further studies are needed on this topic to ascertain whether there are statistically significant differences between the heterologous ROM increases of 8.1% (SMD: 0.72) [23] and 5.0% (SMD: 0.34) [35] respectively versus an average 9.6% (SMD 0.91) increase in the homologous ROM of the other nine studies [24, 26, 27, 28, 29, 30, 31, 32, 33] in this review.

5.0 Conclusions

Non-local (crossover or global) stretching effects derived from unilateral **passive** static stretching can induce moderate magnitude ROM increases. This augmented **non-local** ROM was not modified by the participant's trained state, sex or stretching intensity. Although not statistically significant, there may be a trend for greater contralateral ROM improvements with longer durations of unilateral stretching. If an individual is involved with rehabilitation and cannot stretch an uninjured limb or does not have the time or inclination to stretch all major muscle groups, even stretching a limited number of muscles will promote acute global increases in ROM.

6.0 Compliance with Ethical Standards

6.1 Funding

No sources of funding were used to assist in the preparation of this article.

6.2 Conflicts of Interest

David G Behm, Shahab Alizadeh, Saman Hadjizadeh Anvar, Ben Drury, Urs Granacher and Jason Moran declare that they have no conflicts of interest relevant to the content of this review.

6.3 Authorship Contributions

DGB, SA, SHA conducted the literature search and collected and collated the data. DGB wrote the first draft of the manuscript. JM analyzed and interpreted the data. BD and UG provided input into the analysis and revised the original manuscript. All authors read and approved the final manuscript.

6.4 Data Availability Statement

All pertinent data is provided in the listed tables (PEDro scale analysis, individual and mean study characteristics and moderator analyses) and figures (PRISMA flow chart and funnel plots).

Figure Legends

Figure 1: PRISMA flow chart illustrating different phases of the search and study selection using the following title based nomenclature: stretch, stretching, flexibility, range of motion, non-local, unilateral, contralateral, ipsilateral, crossover, or remote.

Figure 2: Forest plot of effect of acute stretching on range of motion in healthy adults: Main analysis. CI: confidence interval, IV: inverse variance, ROM: range of motion, SD: standard deviation

Figure 3: Forest plot of effect of acute stretching on range of motion in healthy adults: Moderator variables: Trained versus untrained participants subgroup analysis. CI: confidence interval, IV: inverse variance, ROM: range of motion, SD: standard deviation

Figure 4: Forest plot of effect of acute stretching on range of motion in healthy adults: Moderator variables: maximal and submaximal intensity stretching. CI: confidence interval, IV: inverse variance, ROM: range of motion, SD: standard deviation

Figure 5: Forest plot of effect of acute stretching on range of motion in healthy adults: Moderator variables: Low, medium and high stretch duration subgroup analysis. CI: confidence interval, IV: inverse variance, ROM: range of motion, SD: standard deviation

Figure 6: Forest plot of effect of acute stretching on range of motion in healthy adults: Moderator variables: Sex (male versus male and female participants) subgroup analysis. CI: confidence interval, IV: inverse variance, ROM: range of motion, SD: standard deviation

Table Legends

Table 1: PEDro scale analysis of articles

Table 2: Individual study characteristics

Table 3: Mean study characteristics

Table 4: Moderator analyses for effect of acute **unilateral** stretching on **non-local** range of motion in healthy adults.

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