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Influence of chronic stretching on muscle performance: Systematic review

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ABSTRACT

The aim of the current study was to investigate the influence of chronic stretching on muscle performance (MP) by a systematic review. The search strategy included MEDLINE, PEDro, Cochrane CENTRAL, LILACS, and manual search from inception to June 2016. Randomized and controlled clinical trials, non-randomized, and single group studies that have analyzed the influence of flexibility training (FT) (using any stretching technique) on MP were included. Differently, studies with special populations (children, elderly, and people with any dysfunction/ disease), and articles that have used FT protocols shorter than three weeks or 12 sessions were excluded. The MP assessment could have been performed by functional tests (e.g. jump, sprint, stretch-shortening cycle tasks), isometric contractions, and/or isotonic contractions. Twentyeight studies were included out of 513. Seven studies evaluated MP by stretch-shortening cycle tasks, Ten studies evaluated MP by isometric contractions, and 13 studies assessed MP by isotonic contractions. We were unable to perform a meta-analysis due to the high heterogeneity among the included studies. In an individual study level analysis, we identified that 14 studies found positive effects of chronic stretching on MP. The improvements were observed only in functional tests and isotonic contractions, isometric contractions were not affected by FT. Therefore, FT might have an influence on dynamic MP. However, more studies are necessary to confirm whether FT can positively affect MP.

1. Introduction

Stretching is a fundamental component of most training routines, and it is a strategy generally employed when the goal is to enhance muscle flexibility ([Ayala, Sainz de Baranda, De Ste Croix, & Santonja, 2013; Marshall, Cashman, & Cheema, 2011\)](#page-8-0). Flexibility, which refers to the ability of a muscle (group) to elongate [\(Magnusson, Simonsen, Aagaard, Srensen, & Kjaer, 1996\)](#page-9-0), is an important component of physical fitness, and it has an intimate relation with muscle performance (MP).

Stretching can affect MP in different ways depending on how it is executed. The acute effects of stretching have been widely investigated in the last decade. A considerable amount of original studies ([Costa, Herda, Herda, & Cramer, 2014; Cramer et al., 2007](#page-8-1)), and reviews ([Behm & Chaouachi, 2011; Kay & Blazevich, 2012](#page-8-2)) have evidenced that a bout of stretching may provoke deleterious effects on MP. With respect to the chronic effects of stretching, it is well documented its effectiveness in increasing muscle flexibility ([Medeiros, Cini, Sbruzzi, & Lima, 2016](#page-9-1)). However, the influence of such flexibility improvement on MP remains an issue of debate.

The theories that seek to explain the role of flexibility on MP are suggestive. It is believed that chronic stretching can decrease muscle stiffness ([Wilson, Elliott, & Wood, 1992\)](#page-9-2), induce an increase in $Ca⁺$ within the neuromuscular junction [\(Yamashita,](#page-9-3)

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[Ishii, & Oota, 1992](#page-9-3)), and promote sarcomerogenesis ([De Deyne, 2001\)](#page-8-3). All these factors may contribute to a possible enhancement in MP after flexibility training (FT). In the present review, FT refers to exercise routines involving chronic stretching.

The literature is scarce on this topic, to the best of the authors' knowledge, there are only two review studies ([Rubini,](#page-9-4) [Costa, & Gomes, 2007; Stone et al., 2006](#page-9-4)) that attempted to elucidate the role of FT on MP. However, both studies employed a narrative approach and provided insufficient information on the topic. Furthermore, we are aware of a number of studies that have been published in the last decade. Therefore, a review study with more appropriate methodology would contribute to better understand the relationship between FT and MP. Hence, the purpose of the current investigation is to analyze the influence of FT on MP by means of a systematic literature review.

2. Methods

The current study utilized PRISMA (Preferred Reporting Items for Systematic Review and meta-analyses) guidelines for Systematic Reviews and meta-analysis ([Shamseer et al., 2015\)](#page-9-5).

2.1. Data sources and searches

We searched the following electronic databases (from inception to June 2016): MEDLINE (accessed by PubMed), Physiotherapy Evidence Database (PEDro), The Cochrane Central Register of Controlled Trials (Cochrane CENTRAL), and Centro Latino-Americano e do Caribe de Informação em Ciências da Saúde (LILACS). In addition, we searched the references of published studies. The search comprised the following terms: "Flexibility", "Range of Motion", "Joint Range of Motion", "Joint Flexibility", "Muscle Strength", "Strength, muscle", "Muscle Strength Dynamometer", "Performance, Athletic", "Static Stretching", "PNF stretching", "Muscle Stretching Exercises" combined with a high sensitivity combination of words used in the search for randomized clinical trials ([Robinson & Dickersin, 2002](#page-9-6)). We included publications in English, Spanish, and Portuguese. For the combination of the keywords, we utilized the Boolean terms AND and OR. The complete search strategy used for the MEDLINE database is shown in [Appendix A.](#page-7-0)

2.2. Eligibility criteria

We included randomized clinical trials (RCT), controlled clinical trials (CCT), single group, and nonrandomized studies. We opted for including all types of studies since high-quality articles are scarce in the matter investigated in the present review. We included studies that evaluated the long-term effects of stretching on MP. We included studies that employed the three most common stretching techniques: (1) Dynamic stretching, which involves the execution of movement patterns throughout the available range of motion (ROM) [\(Costa et al., 2014](#page-8-1)); (2) Static stretching (SS), which involves reaching a certain ROM and holding the muscle (group) lengthened for a predetermined period of time ([Bandy & Irion, 1994](#page-8-4)); and (3) Proprioceptive neuromuscular facilitation (PNF) stretching, which uses SS and isometric contractions of the target muscle in a cyclical pattern ([Sharman, Cresswell, & Riek, 2006\)](#page-9-7). Muscle performance could have been evaluated by functional tests that follow the stretch-shortening cycle (SSC) principle, isokinetic dynamometry (isotonic or isometric contraction), or repetition-maximum (RM) testing. The following exclusion criteria were used: (1) samples comprised of people with any disease/dysfunction; (2) FT shorter than three weeks or 12 sessions; (3) samples with mean age under 18 or over 40 years old; (4) non-application of muscle stretching; (5) no assessment of MP.

2.3. Studies selection and data extraction

Two investigators independently evaluated titles and abstracts of all articles identified by the search strategy. All abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were selected for full-text evaluation. In the second phase, the same reviewers independently evaluated the full-text articles and made their selection in accordance with the eligibility criteria. Disagreements between reviewers were solved by consensus or through a third person review. Using standardized forms, the same two reviewers independently conducted data extraction with regard to the methodological characteristics of the studies, number of participants, age, interventions, muscle group evaluated, assessment protocol, and conclusions. Disagreements were also solved by consensus. The main outcome extracted was MP.

2.4. Quality assessment

Study quality assessment included adequate sequence generation, allocation concealment, blinding of outcome assessors, description of losses and exclusions, and intention-to-treat analysis. Use of intention-to-treat analysis was considered as a confirmation on study assessment that the number of participants randomized and the number analyzed were identical, except for patients lost to follow-up or who withdrew consent for study participation. Studies without a clear description of these characteristics were considered as unclear or not reporting the latter. The same two reviewers independently performed the quality assessment.

Fig. 1. Flowchart of the included studies.

3. Results

3.1. Description of studies

The search strategy yielded 513 articles, of which 33 studies were considered as potentially relevant and retrieved for detailed analysis. In the full-text analysis, seven studies were excluded. Hence, 28 studies met the eligibility criteria and were included in the systematic review ($n = 821$). [Fig. 1](#page-2-0) shows the flow diagram of the studies included in this review.

3.2. Risk of bias

Of the studies included in this systematic review, 10.7% presented an adequate sequence generation, 14.2% reported allocation concealment; 25% had blinded assessment of outcomes, 25% described losses to follow-up and exclusions, and 35.7% of the studies used the intention-to-treat principle for statistical analyses ([Appendix B](#page-7-1)).

3.3. Effects of interventions

We were unable to perform statistical analyses due to the high heterogeneity among the included studies. [Tables 1](#page-3-0)–3 summarize the studies' characteristics and their conclusions.

Among all stretching techniques found in the literature, PNF stretching and SS are the most common approaches in both sport and rehabilitation contexts. The mechanisms involved in the flexibility improvements following PNF and SS training are similar. It is been demonstrated that neither PNF ([Chalmers, 2004\)](#page-8-5) nor SS [\(Hayes et al., 2012\)](#page-8-6) seem to induce any neural response after stretching, but both of them provoke viscoelastic adaptations within the MTU ([Kubo, Kanehisa, & Fukunaga, 2002; Rees, Murphy, Watsford,](#page-9-8) [McLachlan, & Coutts, 2007\)](#page-9-8). Therefore, a separate discussion regarding the influence of different types of stretching on MP seems redundant. On the other hand, the results of the studies included in the present review led us to believe that increased flexibility influences MP differently depending on the type of task performed (Butterfi[eld, Leonard, Herzog, & Butter](#page-8-7)field, 2005).

3.3.1. Flexibility training on functional tasks

Seven studies assessed MP using a functional test that followed the SSC principle. Four studies [\(Caplan, Rogers, Parr, & Hayes,](#page-8-8) [2009; Kokkonen, Nelson, Eldredge, & Winchester, 2007; Levenez et al., 2013; Wilson et al., 1992](#page-8-8)) found that an increase in flexibility promotes an increase in MP. One study found partial results ([Hunter & Marshall, 2002\)](#page-8-9), and two studies ([Bazett-Jones,](#page-8-10) [Gibson, & McBride, 2008; Yuktasir & Kaya, 2009](#page-8-10)) found no significant difference when compared stretching group to a control group [\(Table 1\)](#page-3-0).

3.3.2. Flexibility training on isometric contraction

Isometric contraction, which was evaluated by isokinetic dynamometry, was utilized in 10 studies. Two of them ([Handel,](#page-8-11)

Table 1

Characteristics of the studies that utilized stretch-shortening cycle tests.

PNF = Proprioceptive Neuromuscular Facilitation; CMJ = Counter Movement Jump; RM = Repetition Maximum; DP = Drop Jump.

[Horstmann, Dickhuth, & Gülch, 1997; Rees et al., 2007\)](#page-8-11) found that FT improves MP whereas 8 studies [\(Blazevich et al., 2014;](#page-8-12) [Guissard & Duchateau, 2004; Konrad, Gad, & Tilp, 2015; Konrad & Tilp, 2014a, 2014b; Minshull, Eston, Bailey, Rees, & Gleeson,](#page-8-12) [2014\)](#page-8-12) found no significant difference when compared to a control group [\(Table 2\)](#page-4-0).

3.3.3. Flexibility training on isotonic contractions

Of the 25 studies included in the present review, 13 of them evaluated muscle performance through isotonic contractions. All of them assessed concentric contraction whereas only three studies evaluated eccentric contraction.

Regarding concentric contractions, seven studies ([Abdel-aziem & Mohammad, 2012; Chen, Lin, Chen, Lin, & Nosaka, 2011; Chen](#page-8-13) [et al., 2009; Chen, Nosaka, et al., 2011; Handel et al., 1997; Leite et al., 2015; Nelson et al., 2012; Worrell, Smith, & Winegardner,](#page-8-13) [1994\)](#page-8-13) showed that FT improves muscle performance, whereas six studies [\(Ferreira, Teixeira-Salmela, & Guimarães, 2007; LaRoche,](#page-8-14) [Lussier, & Roy, 2008; Marshall et al., 2011; Morton, Whitehead, Brinkert, & Caine, 2011; Simão et al., 2011; Wilson et al., 1992](#page-8-14)) did not find any significant changes when compared either to a control group or a pre moment. All three studies [\(Abdel](#page-8-13)[aziem & Mohammad, 2012; Handel et al., 1997; Worrell et al., 1994](#page-8-13)) that evaluated eccentric contractions showed that FT enhances muscle performance when compared either to a control group or a pre moment.

4. Discussion

4.1. Summary of evidence

In the present review, 14 out of 28 articles showed some evidence that FT might be able to enhance MP. However, there seems to be a considerable difference on the effects of FT on static and dynamic activities, our results indicate that static contractions are not affected by FT. On the other hand, dynamic activities/contractions might respond positively to FT, but the methodological quality of the included studies is debatable, and their controversial results have to be taken into account.

4.2. Mechanisms underpinning the increase in muscle length following FT

In order to understand the mechanisms responsible for the possible enhancement in MP after chronic stretching, it is crucial that

Table 2

Characteristics of the studies that assessed isometric contraction.

PNF = Proprioceptive Neuromuscular Facilitation; ID = Isokinetic Dynamometry; PT = Peak Torque; MVC = Maximal Voluntary Contraction; RM = Repetition Maximum; RFD = Rate of Force Development; RTD = Rate of Torque Development; MIC = Maximal Isometric Force.

we clarify the mechanisms involved in muscle flexibility increase itself. The hypotheses normally used to explain improvements in chronic flexibility are: increase in stretch tolerance ([Konrad et al., 2015\)](#page-9-12), viscoelastic adaptations ([Kubo, Kanehisa,](#page-9-13) [Kawakami, & Fukunaga, 2001; Reid & McNair, 2004\)](#page-9-13), and addition of sarcomeres in series ([Zöllner, Abilez, Böl, & Kuhl, 2012\)](#page-9-14).

Increase in stretch tolerance is a widely accepted theory. It states that an increase in ROM without structural changes in the muscle-tendon unit (MTU) can only be explained by a modification in the perception of the discomfort associated with stretch ([Halbertsma, Van Bolhuis, & Goeken, 1996](#page-8-15)), which may be related to a nociceptive adaptation [\(Magnusson et al., 1996](#page-9-0)).

The fact that neural adaptations are present during regular stretching does not exclude the possibility of viscoelastic within the MTU. Viscoelastic materials have an elastic ability, which enables it to store and release energy [\(Böhm, Cole, Brüggemann, & Ruder,](#page-8-16) [2006\)](#page-8-16), but they also have a viscous component since their response to tensile force is rate and time-dependent [\(Peltonen, Cronin,](#page-9-15) [Stenroth, Finni, & Avela, 2013](#page-9-15)). The viscoelastic variable most evaluated among the studies in this field is passive stiffness, which is the change in passive tension per unit change in length of the muscle ([Ryan et al., 2008\)](#page-9-16). The literature has demonstrated that decreased passive stiffness may contribute to flexibility improvements after FT [\(Guissard & Duchateau, 2004\)](#page-8-17).

Another factor that may be responsible for the increased muscle flexibility after chronic stretching is the addition of sarcomeres in series. Sarcomerogenesis has been confirmed in mathematical models ([Zöllner et al., 2012\)](#page-9-14), animal models studies ([De Jaeger,](#page-8-18) [Joumaa, & Herzog, 2015](#page-8-18)), and tendon transfer approaches ([Boakes, Foran, Ward, & Lieber, 2006](#page-8-19)). However, there is a lack of studies analyzing sarcomerogenesis after chronic stretching in vivo. Evaluations of muscle optimum angle have been performed in an attempt to verify possible adaptations within the sarcomeres [\(Chen, Lin, et al., 2011](#page-8-20)). It is believed that a shift of the optimum angle toward a longer muscle length may be caused by an increase in sarcomeres in series.

4.3. Relationship between increased flexibility and MP

As of this date, there is no information about any relationship between modification in stretch tolerance and MP. On the other hand, the literature has hypothesized that modifications in muscle stiffness and the addition in sarcomeres in series within the muscle may have positive influence on MP (Butterfi[eld et al., 2005; Wilson et al., 1992\)](#page-8-7).

The major elastic component of MTU is the tendon ([Zuurbier, Everard, van der Wees, & Huijing, 1994\)](#page-9-17). Hence, the tendinous tissue is able to store potential energy during eccentric contractions and release this energy during the subsequent concentric contraction ([Ishikawa, Pakaslahti, & Komi, 2007\)](#page-8-21). This phenomenon is known as stretch-shortening cycle (SSC). Activities involving

Table 3

Characteristics of the studies that assessed isotonic contraction.

PNF = Proprioceptive Neuromuscular Facilitation; ID = Isokinetic Dynamometry; Ecc = Eccentric; Conc = Concentric; Isom = isometric; PT = Peak Torque; RM = Repetition Maximum.

SSC are highly influenced by muscle stiffness. It is believed that an increased MTU compliance improves its storage capacity, enhancing performance [\(Wilson et al., 1992](#page-9-2)). Another viscoelastic characteristic that has a great impact on SSC movements, and can be modified by chronic stretching is hysteresis [\(Kubo, 2005\)](#page-9-28). Hysteresis refers to the energy lost as heat during stretching of viscoelastic materials ([Kubo, 2005\)](#page-9-28). Hence, a decrease in hysteresis, provoked by chronic stretching, suggests a reduction in energy dissipation in the MTU, which would increment MP.

Flexibility training seems to increment MP in theory, but that is far from being a reality in practice. Half of the studies included in the present review showed either no effect [\(Bazett-Jones et al., 2008; Yuktasir & Kaya, 2009](#page-8-10)) or partial influence ([Hunter & Marshall,](#page-8-9) [2002\)](#page-8-9) of FT on MP involving SSC. There might be an explanation for those results though. A reasonable explanation for the results from [Yuktasir and Kaya \(2009\)](#page-9-11) might be related to the fact that their training protocol did not include knee extensors stretching. It is known that Rectus Femoris plays an essential role on drop jumps, especially from 60 cm height [\(Peng, Kernozek, & Song, 2011](#page-9-29)), the exact test employed in the above-mentioned study. Thus, the non-utilization of knee extensors stretching may have limited the observation of positive results. Regarding the study from [\(Bazett-Jones et al., 2008](#page-8-10)) it is of interest to note that the authors did not find any improvement in muscle flexibility. Therefore, since no muscle adaptation was observed, an enhancement in MP would be improbable. [Hunter and Marshall \(2002\)](#page-8-9) performed an adequate FT program. The authors concluded that power training seems to be the most effective way of improving jump performance, which is expected considering the principle of specificity. However, the authors reinforce that stretching should not be neglected in training routines, since it seems to provide some positive results in MP, especially in countermovement jump.

Another hypothesis utilized in an attempt to elucidate the increase in MP after FT is the addition of sarcomeres in series. It is speculated that sarcomerogenesis potentiates the force-length relationship, which improves MP, especially in static contractions. However, that was not confirmed in the present review. Ten studies evaluated MP using static contractions. However, only two ([Handel et al., 1997; Rees et al., 2007\)](#page-8-11) showed positives results related to chronic stretching. The lack of effectiveness of stretching might be related to the stretching protocols used among the studies. It is possible that the given stimulus was not sufficient to generate adaptations within the muscle cell [\(Freitas et al., 2015](#page-8-25)), and the increase in muscle flexibility was a result of modification in stretch tolerance [\(Konrad et al., 2015](#page-9-12)). It is worth highlighting that the studies that found improvements in MP employed PNF stretching. Therefore, we cannot disregard the possibility that the improvements in isometric contractions observed may be partly related to some adaptation to the isometric contractions present in PNF stretching. Given the current evidence, flexibility training does not seem to positively influence static MP.

Another advantage of sarcomerogenesis is its capacity to potentiate dynamics activities by increasing muscular contraction velocity ([Lieber & Bodine-Fowler, 1993](#page-9-30)). Thirteen studies assessed MP by dynamic (concentric and eccentric) contractions, and the results were quite heterogeneous. With respect to concentric contraction, seven studies [\(Abdel-aziem & Mohammad, 2012; Chen](#page-8-13) [et al., 2009; Chen, Nosaka, et al., 2011; Chen, Lin, et al., 2011; Handel et al., 1997; Leite et al., 2015; Nelson et al., 2012; Worrell](#page-8-13) [et al., 1994\)](#page-8-13) showed positive results whereas six studies [\(Ferreira et al., 2007; LaRoche et al., 2008; Marshall et al., 2011; Morton](#page-8-14) [et al., 2011; Simão et al., 2011; Wilson et al., 1992\)](#page-8-14) showed no significant improvement in peak torque (PT). It is worth mentioning that most of the studies (five out of six) that did not find improvement in concentric contraction performed the assessment of concentric PT alone. Therefore, the possibility of using potential energy storage after the eccentric load was diminished. Considering that FT may improve muscular energy storage capability [\(Kubo, 2005](#page-9-28)), that might have affected the results.

During eccentric contractions, all three studies ([Abdel-aziem & Mohammad, 2012; Handel et al., 1997; Worrell et al., 1994\)](#page-8-13) that performed this type of test found a significant increase in PT. Eccentric contraction is an integral part of function and it is relevant to both training ([Friedmann-Bette et al., 2010](#page-8-26)) and rehabilitation [\(Alfredson, Pietilä, Jonsson, & Lorentzon, 1998\)](#page-8-27) contexts. Interestingly, the relationship between stretching and eccentric contractions has not been properly addressed in the literature ([Behm,](#page-8-28) [Blazevich, Kay, & McHugh, 2016\)](#page-8-28). Our study provides an indicative that FT may improve eccentric performance. However, this issue needs to be better explored in order to confirm or refute our results.

4.4. Study strengths and limitations

To the best of the authors' knowledge, this is the first review to systematically analyze the influence of chronic stretching on MP. The current review presents relevant methodological strengths such as the analysis of two of the most important components of physical fitness: muscle flexibility and muscle strength. Moreover, a strategy for a sensitive and comprehensive search to assure the location of all studies in this field was held. The low methodological quality of the included studies must be pointed as a relevant limitation. The majority of the studies failed to explain the generation of the random sequence. Only six studies blinded the outcome assessors. None of the included studies presented all the items in the risk of bias analysis. It is crucial that future investigations show greater concern about the internal validity in order to improve the data reliability.

5. Conclusion

Flexibility is an essential component of physical fitness, and as such, it should be taken into account in both training and rehabilitation programs. However, The real influence of increased flexibility on MP remains uncertain. Indeed, more than half of the studies included in this review showed some improvement in MP after FT, but it is still unclear how the relationship between those two variables works. It seems like activities where concentric contraction occurs right after the eccentric phase (as in SSC activities) tend to benefit from a higher flexibility level. On the other hand, static contractions seem not to be affected by FT. Definitely, there is a need for more high-quality studies on this topic. Future investigations should invest in establishing how FT affects different types of

activities (dynamic vs. static) to help to elucidate whether FT is a worthwhile alternative.

Disclosures

No funding was received for the current study, and the authors declare no conflict of interest.

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Appendix A. Complete search strategy used for MEDLINE.

- #1 "Muscle Strength"[Mesh] OR "Strength, muscle" OR "Muscle Strength Dynamometer"[Mesh] OR "Dynamometer, Muscle Strength" OR "Dynamometers, Muscle Strength" OR "Muscle Strength Dynamometers" OR "Athletic Performance"[Mesh] OR "Athletic Performances" OR "Performance, Athletic" OR "Performances, Athletic" OR "Sports Performance" OR "Performance, Sports" OR "Performances, Sports" OR "Sports Performances"
- #1 "Muscle Strength"[Mesh] OR "Strength, muscle" OR "Muscle Strength Dynamometer"[Mesh] OR "Dynamometer, Muscle Strength" OR "Dynamometers, Muscle Strength" OR "Muscle Strength Dynamometers" OR "Athletic Performance"[Mesh] OR "Athletic Performances" OR "Performance, Athletic" OR "Performances, Athletic" OR "Sports Performance" OR "Performance, Sports" OR "Performances, Sports" OR "Sports Performances"
- #2 "Muscle Stretching Exercises"[Mesh] OR "Exercise, Muscle Stretching" OR "Exercises, Muscle Stretching" OR "Muscle Stretching Exercise" OR "Dynamic Stretching" OR "Stretching, Dynamic" OR "Isometric Stretching" OR "Stretching, Isometric" OR "Active Stretching" "Stretching, Active" OR "Static-Active Stretching" OR "Static Active Stretching" OR "Stretching, Static-Active" OR "Static Stretching" OR "Stretching, Static" OR "Passive Stretching" OR "Stretching, Passive" OR "Relaxed Stretching" OR "Stretching, Relaxed" OR "Static-Passive Stretching" OR "Static Passive Stretching" OR "Stretching, Static-Passive" OR "Ballistic Stretching" OR "Stretching, Ballistic" OR "Proprioceptive Neuromuscular Facilitation (PNF) Stretching"
- #3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation [mh] OR double-blind method[mh] OR single-blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR ("clinical trial"[tw]) OR ((singl * [tw] OR doubl * [tw] OR trebl∗[tw] OR tripl * [tw]) AND (mask * [tw] OR blind * [tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo * [tw] OR random * [tw] OR research design[mh:noexp] OR follow-up studies [mh] OR prospective studies[mh] OR cross-over
- #4 #1 AND #2 AND #3

Appendix B. Risk of bias of the included studies.

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